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(54) Title: **STIMULATION FOR TREATING AND DIAGNOSING CONDITIONS**

(57) Abstract: Apparatus (4) for treating a subject is provided, including an elongated generally rigid support element (8) having a length of at least 1.8 cm, and having a distal end (9). The apparatus (4) also includes one or more electrodes (10) fixed to the support element (8) in a vicinity of the distal end (9) thereof, and configured to be positioned in a vicinity of a site of the subject when the support element (8) is inserted into a body of the subject, such that a portion of the support element (8) remains outside of the body, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) (6) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG (6) of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject. The apparatus further includes a control unit (7), coupled to the support element (8), and adapted to drive the electrodes (10) to apply an electrical current to the site, and to configure the current to increase cerebral blood flow (CBF) of the subject, so as to treat a condition of the subject.

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STIMULATION FOR TREATING AND DIAGNOSING CONDITIONS

CROSS-REFERENCES TO RELATED APPLICATIONS

The present application claims priority from US Patent Application 10/783,113, filed February 20, 2004, entitled, "Stimulation for acute conditions," which: (a) is a
5 continuation-in-part of US Patent Application 10/258,714, filed October 25, 2002, entitled, "Method and apparatus for stimulating the sphenopalatine ganglion to modify properties of the BBB and cerebral blood flow," which is the US National Phase of PCT Application PCT/IL01/00402, filed May 7, 2001, which claims priority from US
Provisional Patent Application 60/203,172, filed May 8, 2000; and (b) claims priority
10 from US Provisional Patent Application 60/506,165, filed September 26, 2003, entitled, "Diagnostic applications of stimulation."

Each of the above-cited patent applications is assigned to the assignee of the present patent application and is incorporated herein by reference.

FIELD OF THE INVENTION

15 The present invention relates generally to medical procedures and devices. More specifically, the invention relates to the use of electrical, magnetic, electromagnetic, chemical, and/or mechanical stimulation for treating and/or diagnosing medical conditions.

BACKGROUND OF THE INVENTION

20 The blood-brain barrier (BBB) is a unique feature of the central nervous system (CNS) which isolates the brain from the systemic blood circulation. To maintain the homeostasis of the CNS, the BBB prevents access to the brain of many substances circulating in the blood.

The BBB is formed by a complex cellular system of endothelial cells, astroglia,
25 pericytes, perivascular macrophages, and a basal lamina. Compared to other tissues, brain endothelia have the most intimate cell-to-cell connections: endothelial cells adhere strongly to each other, forming structures specific to the CNS called "tight junctions" or zonula occludens. They involve two opposing plasma membranes which form a membrane fusion with cytoplasmic densities on either side. These tight junctions prevent

cell migration or cell movement between endothelial cells. A continuous uniform basement membrane surrounds the brain capillaries. This basal lamina encloses contractile cells called pericytes, which form an intermittent layer and probably play some role in phagocytosis activity and defense if the BBB is breached. Astrocytic end
5 feet, which cover the brain capillaries, build a continuous sleeve and maintain the integrity of the BBB by the synthesis and secretion of soluble growth factors (e.g., gamma-glutamyl transpeptidase) essential for the endothelial cells to develop their BBB characteristics.

PCT Patent Publication WO 01/85094 to Shalev and Gross, which is assigned to
10 the assignee of the present patent application and is incorporated herein by reference, describes apparatus for modifying a property of a brain of a patient, including electrodes applied to a sphenopalatine ganglion (SPG) or a neural tract originating in or leading to the SPG. A control unit drives the electrodes to apply a current capable of inducing (a) an increase in permeability of a blood-brain barrier (BBB) of the patient, (b) a change in
15 cerebral blood flow of the patient, and/or (c) an inhibition of parasympathetic activity of the SPG.

US Patent 5,756,071 to Mattern et al., which is incorporated herein by reference, describes a method for nasally administering aerosols of therapeutic agents to enhance penetration of the blood brain barrier. The patent describes a metering spray designed
20 for per nasal application, the spray containing at least one sex hormone or at least one metabolic precursor of a sex hormone or at least one derivative of a sex hormone or combinations of these, excepting the precursors of testosterone, or at least one biogenic amine, with the exception of catecholamines.

US Patent 5,752,515 to Jolesz et al., which is incorporated herein by reference,
25 describes apparatus for image-guided ultrasound delivery of compounds through the blood-brain barrier. Ultrasound is applied to a site in the brain to effect in the tissues and/or fluids at that location a change detectable by imaging. At least a portion of the brain in the vicinity of the selected location is imaged, e.g., via magnetic resonance imaging, to confirm the location of that change. A compound, e.g., a
30 neuropharmaceutical, in the patient's bloodstream is delivered to the confirmed location by applying ultrasound to effect opening of the blood-brain barrier at that location and, thereby, to induce uptake of the compound there.

US Patent 6,526,318 to Ansarinia and related PCT Publication WO 01/97905 to Ansarinia, which are incorporated herein by reference, describe a method for the suppression or prevention of various medical conditions, including pain, movement disorders, autonomic disorders, and neuropsychiatric disorders. The method includes
5 positioning an electrode on or proximate to at least one of the patient's SPG, sphenopalatine nerves, or vidian nerves, and activating the electrode to apply an electrical signal to such nerve. In a further embodiment for treating the same conditions, the electrode used is activated to dispense a medication solution or analgesic to such nerve. The '318 patent and '905 publication also describe surgical techniques for
10 implanting the electrode.

US Patent 6,405,079 to Ansarinia, which is incorporated herein by reference, describes a method for the suppression or prevention of various medical conditions, including pain, movement disorders, autonomic disorders, and neuropsychiatric disorders. The method includes positioning an electrode adjacent to or around a sinus,
15 the dura adjacent a sinus, or falx cerebri, and activating the electrode to apply an electrical signal to the site. In a further embodiment for treating the same conditions, the electrode dispenses a medication solution or analgesic to the site. The '079 patent also describes surgical techniques for implanting the electrode.

PCT Publications WO 03/084591, WO 03/020350, WO 03/000310, WO
20 02/068031, and WO 02/068029 to Djupesland, which are incorporated herein by reference, describe nasal delivery devices. US Patent Application Publication 2003/0079742 to Giroux, which is incorporated herein by reference, describes a nasal nebulizer.

US Patents 5,725,471 and 6,086,525 to Davey et al., which are incorporated
25 herein by reference, describe a magnetic nerve stimulator system comprising a core of highly saturable material with a coil winding. A thyristor capacitive discharge circuit pulses the device. A rapidly changing magnetic field is guided by the core, preferably vanadium permendur. A C-shape is employed for focusing the stimulation.

PCT Publication WO 02/32504 to Zanger et al., which is incorporated herein by
30 reference, describes a transcranial magnetic stimulation (TMS) device for treating certain physiological conditions, such as cardiovascular or neurophysiological conditions, or for studying the physiology of the body.

US Patent Application Publication 2003/0050527 to Fox et al., which is incorporated herein by reference, describes apparatus and methods for delivery of TMS. The apparatus includes a TMS coil which when energized generates an electric field substantially parallel to a long axis of the coil and substantially normal to a surface of the coil.

US Patent 6,432,986 to Levin and PCT Publication WO 99/03473 to Levin, which are incorporated herein by reference, describe techniques for inhibiting a cerebral neurovascular disorder or a muscular headache. The techniques include intranasally administering a pharmaceutical composition comprising a long-acting local anesthetic.

US Patent 6,491,940 to Levin, US Patent Application 2003/0133877 to Levin, and PCT Publication WO 00/44432 to Levin, which are incorporated herein by reference, describe techniques for inhibiting a cerebral neurovascular disorder or a muscular headache. The techniques include intranasally administering a pharmaceutical composition comprising a long-acting local anesthetic. Apparatus for delivering or applying the composition is also described.

US Patent Application 2001/0004644 to Levin and PCT Publication WO 01/43733 to Levin, which are incorporated herein by reference, describe techniques for inhibiting cephalic inflammation, including meningeal inflammation and cerebral inflammation. The techniques include intranasally administering a long-acting local anesthetic. Apparatus for delivering or applying the composition is also described, including a dorsonasally implanted electronic neural stimulator, such as a transepithelial neural stimulation device.

An article entitled "Endoscopic transnasal neurolytic sphenopalatine ganglion block for head and neck cancer pain," by Varghese et al., J Laryngol Otol. 2001 May; 115(5):385-7, which is incorporated herein by reference, describes nasal endoscopy as a valuable adjunct to the localization of the sphenopalatine ganglion. Twenty-two patients with advanced malignancies of the head and neck region whose pain was not adequately controlled with conventional medications, including oral morphine, were given nasal endoscopically-guided neurolytic sphenopalatine ganglion block with six per cent phenol, after a prognostic block with local anesthetic solution. Seventeen patients had good immediate relief. One had partial relief and four had inadequate relief. On follow-

up for one month, the patients had significantly lower pain intensity and the pain was more manageable with oral medication.

US Patent Application Publication 2002/0052311 to Solomon et al., which is incorporated herein by reference, describes methods for treating and/or diagnosing neurological conditions of the CNS. Some embodiments include displaying a therapeutic molecule capable of treating the condition on a viral display vehicle and introducing the vehicle into a subject in need thereof by applying the viral display vehicle to an olfactory system of the subject.

PCT Publication WO 02/094191 to Wisniewski et al., which is incorporated herein by reference, describes techniques for diagnosing Alzheimer's disease in vivo using magnetic resonance imaging. A labeled A-beta peptide or its derivative is injected into the patient to be diagnosed, after which the patient is subjected to magnetic resonance imaging.

US Patent 5,059,415 to Neuwelt, which is incorporated herein by reference, describes a method for diagnosing and characterizing brain lesions by first chemically modifying the blood-brain barrier (BBB) in order to increase BBB permeability. Thereafter, a chemical agent (e.g., mAb or pAb) is introduced which binds to brain lesions.

US Patent 4,866,042 to Neuwelt, which is incorporated herein by reference, describes a method for treating genetic and acquired brain disorders by introducing genetic material into the blood stream for delivery to the brain. Prior to delivery, the interendothelial structure of the BBB is chemically altered to permit passage of the genetic material therethrough.

US Patent 6,117,454 to Kreuter et al., which is incorporated herein by reference, describes a method for delivering drugs and diagnostics across the BBB or blood-nerve barrier by incorporating these agents into nanoparticles which have been fabricated in conventional ways and then coated with an additional surfactant.

PCT Publication WO 00/73343 to Soreq et al., which is incorporated herein by reference, describes techniques for diagnosing CNS stress, elevated glucocorticoid level, disruption of the blood-brain barrier or Alzheimer's disease, by testing a blood sample

using antibodies recognizing acetylcholinesterase or a C-terminal peptide derived from acetylcholinesterase.

US Patent 5,268,164 to Kozarich et al., which is incorporated herein by reference, describes techniques for using polypeptides called receptor mediated
5 permeabilizers to increase the permeability of the blood-brain barrier to molecules such as therapeutic agents or diagnostic agents.

US Patent 6,005,004 to Katz et al., which is incorporated herein by reference, describes site-specific biomolecular complexes comprising a therapeutic, prophylactic and diagnostic agent, and an omega-3 fatty acid and derivatives thereof, which
10 complexes are covalently bonded with cationic carriers and permeabilizer peptides for delivery across the BBB and with targeting moieties for uptake by target brain cells.

US Patent 5,833,988 to Friden, which is incorporated herein by reference, describes a method for delivering a neuropharmaceutical or diagnostic agent across the BBB to the brain. The method comprises administering to the host a therapeutically
15 effective amount of an antibody-neuropharmaceutical or diagnostic agent conjugate wherein the antibody is reactive with a transferrin receptor.

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SUMMARY OF THE INVENTION

In some embodiments of the present invention, an acute and/or emergency medical condition of a subject is treated by stimulating at least one "modulation target

site" (MTS), as defined hereinbelow, by applying electrical, magnetic, electromagnetic, chemical, and/or mechanical stimulation to the site. Such treatment is typically applied as soon as possible after diagnosis of the condition, such as in an emergency room or wherever the subject happens to be. For some conditions, such as acute brain injury
5 (e.g., ischemic stroke, vasospasm following subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), or seizure), the stimulation is configured so as to dilate cerebral vessels, thereby increasing blood flow to affected brain tissue and tissue in a vicinity thereof, and decreasing damage caused by the condition. For other conditions, such as occlusion within the retinal circulation, the stimulation is configured so as to dilate blood
10 vessels, thereby increasing retinal blood flow and treating the condition. For treating complications of SAH, the stimulation is typically applied after surgery has been performed to treat an aneurysm that caused the SAH; the stimulation counteracts the reduced cerebral blood flow (CBF) sometimes caused by blood passage into the subarachnoid space.

15 In the present patent application, a "modulation target site" (MTS) consists of:

- a sphenopalatine ganglion (SPG) (also called a pterygopalatine ganglion);
- a nerve of the pterygoid canal (also called a vidian nerve), such as a greater superficial petrosal nerve (a preganglionic parasympathetic
20 nerve) or a lesser deep petrosal nerve (a postganglionic sympathetic nerve);
- a greater palatine nerve;
- a lesser palatine nerve;
- a sphenopalatine nerve;
- 25 • a communicating branch between the maxillary nerve and the sphenopalatine ganglion;
- an otic ganglion;
- an afferent fiber going into the otic ganglion;
- an efferent fiber going out of the otic ganglion; or
- 30 • an infraorbital nerve.

In some embodiments of the present invention, electrical stimulation is applied to the SPG system, as defined hereinbelow, and/or to at least one other appropriate MTS, using a substantially rigid support element comprising one or more electrodes, adapted to be quickly inserted into the site and removed upon completion of the acute treatment.

- 5 For applications in which the MTS includes an SPG of the subject, the support element is typically inserted, (a) via the nose, through the sphenopalatine foramen, or (b) via the roof of the oral cavity, through the greater palatine canal. The support element typically comprises a mark or stopper that indicates the point at which the support element has been sufficiently inserted via the appropriate foramen.

- 10 In the present patent application, "SPG system" means the SPG and associated neuroanatomical structures, including neural tracts originating in or reaching the SPG, including outgoing and incoming parasympathetic and sympathetic tracts, which tracts include preganglionic fibers of the SPG (e.g., fibers contained within the vidian nerve) and postganglionic fibers of the SPG (fibers that travel anterogradely from the SPG
15 toward the brain vascular bed, including the retro-orbital branches of the SPG, which are fibers that connect the SPG with orbital neural structures).

- In some embodiments of the present invention, magnetic stimulation is applied to at least one MTS using a magnetic induction device that comprises a control unit, and at least one coil that is adapted to be placed in a vicinity of the MTS. For some
20 applications, e.g., in which the MTS includes an SPG of the subject, the coil is adapted to be inserted into a nasal cavity of the subject. Alternatively, the coil is adapted to be placed in a vicinity of a temporomandibular joint, in a vicinity of the MTS. Further alternatively, the coil is adapted to be placed completely or partially around the head, and to focus the magnetic field on the MTS.

- 25 In some embodiments of the present invention, chemical stimulation of the SPG system, and/or of at least one other appropriate MTS, is achieved by presenting chemicals, for example in a liquid or gaseous state, to an air passage of the subject, such as a nasal cavity or a throat, or in a vicinity thereof. The temporal profile and other quantitative characteristics of such chemical modulation are believed by the present
30 inventors to have a mechanism of action that has a neuroanatomical basis overlapping with that of the electrical modulation of the MTS. Furthermore, experimental animal evidence collected by the inventors and described in US Provisional Patent Application

60/368,657 to Shalev and Gross entitled, "SPG stimulation," filed March 28, 2002, which is assigned to the assignee of the present invention and is incorporated herein by reference, suggest a correlation between the mechanisms of increasing cerebral blood flow and increased cerebrovascular permeability. For some applications, chemical-
5 presentation techniques described herein are practiced in combination with techniques described in US Provisional Patent Application 60/376,048, filed April 25, 2002, entitled, "Methods and apparatus for modifying properties of the BBB and cerebral circulation by using the neuroexcitatory and/or neuroinhibitory effects of odorants on nerves in the head," which is assigned to the assignee of the present patent application
10 and is incorporated herein by reference.

Chemicals that may increase or decrease cerebral blood flow and/or the permeability of the blood-brain barrier (e.g., via modulation of SPG-related fibers), include, but are not limited to, propionic acid, cyclohexanone, amyl acetate, acetic acid, citric acid, carbon dioxide, sodium chloride, ammonia, menthol, alcohol, nicotine,
15 piperine, gingerol, zingerone, allyl isothiocyanate, cinnamaldehyde, cuminaldehyde, 2-propenyl/2-phenylethyl isothiocyanate, thymol, and eucalyptol. The chemicals reach the appropriate neural structures and induce vasodilatation, vasoconstriction and/or cerebrovascular permeability changes.

In some embodiments of the present invention, chemical stimulation is applied to
20 the SPG system, and/or to at least one other appropriate MTS, using (a) a nasal applicator adapted to deliver the stimulating chemical to an upper region of the nasal cavity, or (b) a transpalatine applicator inserted via the greater palatine canal.

In some embodiments of the present invention, stimulation of the MTS is achieved by applying mechanical stimulation to the MTS, e.g., vibration.

25 In some embodiments of the present invention, stimulation of at least one MTS is achieved by applying a neuroexcitatory agent to the MTS. Suitable neuroexcitatory agents include, but are not limited to, acetylcholine and urocholine. For some applications, the MTS is stimulated by applying a neuroinhibitory agent, such as atropine, hexamethonium, or a local anesthetic (e.g., lidocaine).

30 In some embodiments of the present invention, the short-term MTS stimulation techniques described herein are used in order to facilitate a diagnosis of a condition of the central nervous system (CNS). For some applications, stimulation of the MTS

enhances delivery of diagnostic molecules across the BBB by modulation of at least one MTS and/or another parasympathetic center. These techniques typically stimulate the nerve fibers of the MTS, thereby inducing the middle and anterior cerebral arteries to dilate, and also result in increased CNS bioavailability of various compounds. In this manner, the movement of large diagnostic molecules from within blood vessels to the CNS parenchyma, is substantially increased.

For other applications, stimulation of the MTS enhances clearance of at least one constituent of the CNS, such as a protein, from the CNS, across the BBB, and into the systemic blood circulation of the subject. Once the constituent is in the blood circulation, a conventional blood assay is performed in order to detect the constituent. In the absence of the increased permeability of the BBB caused by the stimulation techniques described herein, these constituents do not generally cross the BBB to the blood circulation in quantities sufficient for accurate detection and diagnosis.

In some embodiments of the present invention, an SPG of the subject is indirectly activated by stimulating afferent fibers of the trigeminal nerve (cranial nerve V) of the subject, either electrically, magnetically, or electromagnetically. A reflex response to such stimulation leads to activation of the SPG. (For example, the maxillary branch of the trigeminal nerve directly contacts the SPG.) Typically, but not necessarily, such stimulation is performed while the subject is under general anesthesia or sedation. For some applications, cranial nerve V is stimulated by non-invasively attaching electrodes to the surface of the face of the subject, typically using techniques commonly used for transcutaneous electrical nerve stimulation (TENS). For example, TENS may be applied to a cheek or a tip of a nose of a subject.

In an embodiment of the present invention, an oral appliance is provided that is adapted to be brought into contact with a mucous membrane of a palate of an oral cavity of a subject. The appliance comprises one or more electrodes, which are driven to apply transmucosal electrical stimulation to nerve fibers within or immediately above the mucous membrane, which fibers directly innervate an SPG of the subject. Typically, but not necessarily, such stimulation is performed while the subject is under general anesthesia or sedation. Such transmucosal stimulation may require less current than the transcutaneous stimulation described hereinabove.

It is to be appreciated that references herein to specific modulation target sites are to be understood as including other modulation target sites, as appropriate.

It is further to be appreciated that insertion and modulation sites, methods of insertion and/or implantation, and parameters of modulation are described herein by way of illustration and not limitation, and that the scope of the present invention includes
5 other possibilities which would be obvious to someone of ordinary skill in the art who has read the present patent application.

It is yet further to be appreciated that while some embodiments of the invention are generally described herein with respect to electrical transmission of power and
10 electrical modulation of tissue, other modes of energy transport may be used as well. Such energy includes, but is not limited to, direct or induced electromagnetic energy, radiofrequency (RF) transmission, mechanical vibration, ultrasonic transmission, optical power, and low power laser energy (via, for example, a fiber optic cable).

It is additionally to be appreciated that whereas some embodiments of the present
15 invention are described with respect to application of electrical currents to tissue, this is to be understood in the context of the present patent application and in the claims as being substantially equivalent to applying an electrical field, e.g., by creating a voltage drop between two electrodes.

In embodiments of the present invention, at least one "modulation target
20 location" (MTL), as defined hereinbelow, is stimulated in order to facilitate a diagnosis of a condition of a central nervous system (CNS) of a subject. The MTL is typically stimulated by applying electrical, chemical, mechanical and/or odorant stimulation to the location. Such stimulation is configured to increase the permeability of the blood-brain barrier (BBB) in order to increase the transport of (a) a diagnostic agent from the
25 systemic blood circulation of the subject into the CNS, and/or (b) a constituent of the CNS, such as a biochemical agent, from the CNS into the systemic circulation. The electrical, chemical, mechanical and odorant stimulation techniques described herein may facilitate the diagnosis of a number of CNS conditions, including, but not limited to, neurodegenerative conditions (e.g., Alzheimer's disease, Parkinson's Disease, and
30 ALS), neoplastic processes (either primary or metastatic), immune- and autoimmune-related disorders (e.g., HIV and multiple sclerosis), and CNS inflammatory processes.

In the present patent application, a "modulation target location" (MTL) consists of:

- a sphenopalatine ganglion (SPG) (also called a pterygopalatine ganglion);
- 5 • an anterior ethmoidal nerve;
- a posterior ethmoidal nerve;
- a communicating branch between the anterior ethmoidal nerve and the SPG (retro-orbital branch);
- a communicating branch between the posterior ethmoidal nerve and the
10 SPG (retro-orbital branch);
- a nerve of the pterygoid canal (also called a vidian nerve), such as a greater superficial petrosal nerve (a preganglionic parasympathetic nerve) or a lesser deep petrosal nerve (a postganglionic sympathetic nerve);
- 15 • a greater palatine nerve;
- a lesser palatine nerve;
- a sphenopalatine nerve;
- a communicating branch between the maxillary nerve and the sphenopalatine ganglion;
- 20 • a nasopalatine nerve;
- a posterior nasal nerve;
- an infraorbital nerve;
- an otic ganglion;
- an afferent fiber going into the otic ganglion; and/or
- 25 • an efferent fiber going out of the otic ganglion.

The stimulation techniques described herein typically enhance delivery of diagnostic and biochemical molecules across the BBB by stimulating the nerve fibers of the MTL, thereby inducing the middle and anterior cerebral arteries to dilate, for

example, and also causing the walls of these cerebral arteries to become more permeable to large molecules. In this manner, the movement of large molecules from within blood vessels to the cerebral tissue, and from the cerebral tissue to blood vessels, is substantially increased. Without the use of the techniques described herein or functional
5 equivalents thereof, the intact BBB generally blocks or substantially reduces the passage of such molecules.

In some embodiments of the present invention, stimulation of an MTL is configured to increase the transport of a diagnostic agent across the BBB from the systemic blood circulation into the CNS. Prior to, during, or after such stimulation, the
10 diagnostic agent is administered to a non-CNS tissue of the subject, typically the systemic blood circulation, such as intravenously, and a diagnostic procedure, typically an imaging modality, is then performed directly on the CNS. The diagnostic agent is typically a contrast agent or enhancer, or a tracer, such as a radioisotope. For example, an imaging procedure may be performed by intravenously administering labeled (e.g.,
15 radiolabeled) beta-Amyloid monoclonal antibody (mAb) or polyclonal antibody (pAb), stimulating an MTL to transport the tracer across the BBB, and mapping the distribution of the tracer in the brain using Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) imaging.

These techniques for facilitating the transport of diagnostic agents into the CNS
20 generally increase the accuracy of CNS diagnostic procedures. Such increased accuracy is obtained in part because a greater amount of the agent enters the CNS as a result of the MTL stimulation. Additionally, MTL stimulation allows diagnostic agents having greater molecular weights to cross the BBB, which enables the effective use of a broader range of agents having greater specificity, such as labeled antibodies and cytokines. The
25 greater diagnostic sensitivity of these techniques also may allow the performance of a non-invasive imaging procedure instead of a more invasive procedure, such as sampling of CNS tissue or fluid (e.g., cerebrospinal fluid (CSF) lumbar puncture, brain biopsy).

In other embodiments of the present invention, stimulation of an MTL is configured to increase the transport of a biochemical agent across the BBB from the
30 CNS to a non-CNS tissue of the subject, such as the systemic blood circulation. Such biochemical agents are typically disease-specific biochemical markers. Prior to stimulation of an MTL to increase BBB permeability, the concentration of such a

biochemical agent is typically greater in the CNS than in the systemic circulation, i.e., there is a concentration gradient across the endothelium. Therefore, increasing the permeability of the BBB generally releases the agent into the systemic circulation. Once in the systemic circulation, diagnosis is typically performed by sampling a body fluid, typically blood, and analyzing the whole blood, plasma, or serum.

These techniques for facilitating the transport of biochemical agents from the CNS into the systemic circulation generally increase the rate of transfer and, consequently, the amount of the agent in the systemic circulation. The diagnostic signal, i.e., the statistical sample size, of the agent in the circulation is thereby increased, generally resulting in increased accuracy of the diagnostic procedure. Additionally, for some CNS conditions, use of these techniques may allow the performance of a minimally-invasive procedure instead of a more invasive procedure, such as sampling of CNS tissue or fluid (e.g., CSF lumbar puncture, brain biopsy).

In some embodiments of the present invention, stimulation of at least one MTL is achieved by presenting odorants to an air passage of a patient, such as a nasal cavity or the throat, so as to facilitate a diagnosis of a CNS condition. The temporal profile and other quantitative characteristics of such odorant modulation are believed by the present inventors to have a mechanism of action that has a neuroanatomical basis overlapping with that of the electrical modulation of the SPG or another MTL. Furthermore, experimental animal evidence collected by the inventors and described in US Provisional Patent Application 60/368,657 to Shalev and Gross entitled, "SPG stimulation," filed March 28, 2002, which is assigned to the assignee of the present invention and is incorporated herein by reference, suggest a correlation between the mechanisms of increasing cerebral blood flow and increased cerebrovascular permeability. For some applications, odorant-presentation techniques for facilitating a diagnosis described herein are practiced in combination with techniques described in US Provisional Patent Application 60/376,048, filed April 25, 2002, entitled, "Methods and apparatus for modifying properties of the BBB and cerebral circulation by using the neuroexcitatory and/or neuroinhibitory effects of odorants on nerves in the head," which is assigned to the assignee of the present patent application and is incorporated herein by reference.

Odorants that may increase or decrease cerebral blood flow and/or the permeability of the BBB, and which are suitable for facilitating a diagnosis of a CNS condition, include, but are not limited to, propionic acid, cyclohexanone, amyl acetate, acetic acid, citric acid, carbon dioxide, sodium chloride, ammonia, menthol, alcohol, nicotine, piperine, gingerol, zingerone, allyl isothiocyanate, cinnamaldehyde, cuminaldehyde, 2-propenyl/2-phenylethyl isothiocyanate, thymol, and eucalyptol.

The odorants reach the appropriate neural structures and induce vasodilatation, vasoconstriction and/or cerebrovascular permeability changes. Delivery of a diagnostic agent to the CNS can be achieved by mixing the agent with the odorant; by intravenously, intraperitoneally, or intramuscularly administering the agent while the odorant is having an effect, or therebefore; or by other delivery methods known in the art.

In some embodiments of the present invention, stimulation of at least one MTL is achieved by applying a neuroexcitatory agent to the MTL. Suitable neuroexcitatory agents include, but are not limited to, acetylcholine and urocholine. For some applications, the MTL is stimulated by applying a neuroinhibitory agent, such as atropine, hexamethonium, or a local anesthetic (e.g., lidocaine).

In some embodiments of the present invention, stimulation of the MTL is achieved by applying mechanical stimulation to the MTL, e.g., vibration.

It is to be appreciated that references herein to specific modulation target locations are to be understood as including other modulation target locations, as appropriate.

It is further to be appreciated that implantation and modulation locations, methods of implantation, and parameters of modulation are described herein by way of illustration and not limitation, and that the scope of the present invention includes other possibilities which would be obvious to someone of ordinary skill in the art who has read the present patent application.

It is yet further to be appreciated that while some embodiments of the invention are generally described herein with respect to electrical transmission of power and electrical modulation of tissue, other modes of energy transport may be used as well. Such energy includes, but is not limited to, direct or induced electromagnetic energy,

radiofrequency (RF) transmission, mechanical vibration, ultrasonic transmission, optical power, and low power laser energy (via, for example, a fiber optic cable).

It is additionally to be appreciated that whereas some embodiments of the present invention are described with respect to application of electrical currents to tissue, this is to be understood in the context of the present patent application and in the claims as being substantially equivalent to applying an electrical field, e.g., by creating a voltage drop between two electrodes.

As used in the present patent application, including the claims, the central nervous system (CNS) is to be understood as consisting of CSF, the brain, and the spinal cord.

There is therefore provided, in accordance with an embodiment of the present invention, apparatus for treating a subject, including:

an elongated generally rigid support element having a length of at least 1.8 cm, and having a distal end;

one or more electrodes fixed to the support element in a vicinity of the distal end thereof, and configured to be positioned in a vicinity of a site of the subject when the support element is inserted into a body of the subject, such that a portion of the support element remains outside of the body, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

a control unit, coupled to the support element, and adapted to drive the electrodes to apply an electrical current to the site, and to configure the current to increase cerebral blood flow (CBF) of the subject, so as to treat a condition of the subject.

For some applications, the condition includes one or more of the following, and the control unit is adapted to configure the current to increase the CBF to a level sufficient to treat the condition:

- an acute ischemic condition of a brain of the subject;
- a complication of subarachnoid hemorrhage (SAH) of the subject;
- an acute brain injury of the subject;
- vasospasm after stroke of the subject;
- 5 • traumatic brain injury (TBI) of the subject;
- a seizure of the subject;
- occlusion within a retinal circulation of the subject;
- retinal artery occlusion (RAO) of the subject; and/or
- retinal venous occlusion (RVO) of the subject.

10 In an embodiment, the site includes the SPG of the subject, and the electrodes are configured to be positioned in the vicinity of the SPG.

For some applications, the support element is substantially straight. For some applications, the support element has a length between about 7 cm and about 13 cm. For some applications, a portion of the support element adapted for insertion into the body

15 has a length of between about 2.5 cm and about 3 cm.

For some applications, the control unit is adapted to configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2

20 minutes, and off periods of between about 1 second and about 2 minutes.

In an embodiment, the support element is adapted to be positioned in the vicinity of the site by insertion through a roof of an oral cavity of the subject. For some applications, the support element is adapted to be positioned in the vicinity of the site by insertion through a greater palatine canal of the subject.

25 In an embodiment, the support element is adapted to be positioned in the vicinity of the site by insertion through a nose of the subject. For some applications, the support element is adapted to be positioned in the vicinity of the site by insertion through a sphenopalatine foramen of the subject.

For some applications, the support element includes at least one mark, adapted to indicate a depth of insertion of the support element in the body. For some applications, a distance of the mark from the distal end of the support element is between about 2.5 cm and about 3 cm.

- 5 For some applications, the support element includes a stopper, adapted to prevent insertion of the support element into the body beyond a certain depth. For some applications, a distance of the stopper from the distal end of the support element is between about 2.5 cm and about 3 cm.

- 10 For some applications, the support element is bent at one or more locations. For some applications, an angle of a bend of the support element is between about 20 and about 40 degrees. For some applications, a distance of a bend of the support element from the distal end of the support element is between about 2 cm and about 3 cm.

- There is further provided, in accordance with an embodiment of the present invention, apparatus for treating a complication of subarachnoid hemorrhage (SAH) of a subject, including:

- 15 a medical vehicle, adapted to directly treat the SAH; and
a stimulator adapted to stimulate at least one site of the subject, so as to treat a complication arising from use of the medical vehicle, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject.

In an embodiment, the site includes the SPG of the subject, and the stimulator is adapted to stimulate the SPG.

In an embodiment, the stimulator is adapted to configure the stimulation to increase cerebral blood flow (CBF) of the subject.

For some applications, the medical vehicle includes a tool for clipping an aneurysm that caused the SAH. Alternatively or additionally, the medical vehicle includes a pharmaceutical composition for treating an aneurysm that caused the SAH.

5 For some applications, the stimulator includes an electrical stimulator, adapted to apply an electrical current to the site. Alternatively or additionally, the stimulator includes a magnetic stimulator, adapted to apply a magnetic field to the site. Further alternatively or additionally, the stimulator includes a chemical stimulator, adapted to apply a chemical to the site. Still further alternatively or additionally, the stimulator includes a mechanical stimulator, adapted to apply mechanical energy to the site.

10 There is also provided, in accordance with an embodiment of the present invention, apparatus for treating a condition of a subject, including:

a coil, adapted to be positioned in a vicinity of a site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

20 a control unit, adapted to drive the coil to generate a magnetic field in the vicinity of the site capable of inducing an increase in cerebral blood flow (CBF) of the subject.

In an embodiment, the site includes the SPG of the subject, and the coil is adapted to be positioned in the vicinity of the SPG.

25 For some applications, the control unit is adapted to generate the magnetic field with a strength sufficient to stimulate the site, and insufficient to substantially stimulate brain tissue of the subject.

For some applications, the apparatus includes a cooling element, adapted to prevent excessive heating of the coil.

30 For some applications, the coil includes between about 4 and about 30 loops of wire.

In an embodiment, the coil is adapted to be inserted into a nasal cavity of the subject.

For some applications, the coil is substantially figure-eight-shaped. Alternatively, the coil is substantially 4-leaf-shaped. Further alternatively, the coil is
5 substantially circular.

For some applications, the coil has a diameter of between about 3 mm and about 12 mm.

In an embodiment, the coil is adapted to be placed in a vicinity of a temporomandibular joint of the subject. For some applications, the coil has a diameter
10 of between about 3 cm and about 12 cm.

In an embodiment, the coil is adapted to be placed around at least a portion of a head of the subject. For some applications, the coil has a diameter of between about 3 cm and about 12 cm.

There is additionally provided, in accordance with an embodiment of the present
15 invention, apparatus for treating a condition of a subject, including:

a coil, adapted to be positioned in a vicinity of a site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic
20 ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

a control unit, adapted to drive the coil to generate a magnetic field in the vicinity
25 of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject.

In an embodiment, the site includes the SPG of the subject, and the coil is adapted to be positioned in the vicinity of the SPG.

For some applications, the control unit is adapted to generate the magnetic field
30 with a strength sufficient to stimulate the site, and insufficient to substantially stimulate brain tissue of the subject.

For some applications, the apparatus includes a cooling element, adapted to prevent excessive heating of the coil.

For some applications, the coil includes between about 4 and about 30 loops of wire.

5 In an embodiment, the coil is adapted to be inserted into a nasal cavity of the subject.

For some applications, the coil is substantially figure-eight-shaped. Alternatively, the coil is substantially 4-leaf-shaped. Further alternatively, the coil is substantially circular. For some applications, the coil has a diameter of between about 3
10 mm and about 12 mm.

In an embodiment, the coil is adapted to be placed in a vicinity of a temporomandibular joint of the subject. For some applications, the coil has a diameter of between about 30 mm and about 120 mm.

In an embodiment, the coil is adapted to be placed around at least a portion of a
15 head of the subject. For some applications, the coil has a diameter of between about 10 cm and about 25 cm.

There is yet additionally provided, in accordance with an embodiment of the present invention, apparatus for facilitating a diagnosis of a condition of a subject, including:

20 an elongated generally rigid support element having a length of at least 1.8 cm, and having a distal end;

one or more electrodes fixed to the support element in a vicinity of the distal end thereof, and configured to be positioned in a vicinity of a site of the subject when the support element is inserted into a body of the subject, such that a portion of the support
25 element remains outside of the body, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an
30 efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the

subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

a control unit, coupled to the support element, and adapted to:

drive the electrodes to apply an electrical current to the site, and

5 configure the current to induce an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a diagnostic agent across the BBB into a central nervous system (CNS) of the subject.

In an embodiment, the site includes the SPG of the subject, and the electrodes are configured to be positioned in the vicinity of the SPG.

10 For some applications, the support element is substantially straight. For some applications, the support element has a length between about 7 cm and about 13 cm. For some applications, a portion of the support element adapted for insertion into the body has a length of between about 2.5 cm and about 3 cm.

15 For some applications, the control unit is adapted to configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

20 In an embodiment, the support element is adapted to be positioned in the vicinity of the site by insertion through a roof of an oral cavity of the subject. For some applications, the support element is adapted to be positioned in the vicinity of the site by insertion through a greater palatine canal of the subject.

25 In an embodiment, the support element is adapted to be positioned in the vicinity of the site by insertion through a nose of the subject. For some applications, the support element is adapted to be positioned in the vicinity of the site by insertion through a sphenopalatine foramen of the subject.

30 For some applications, the support element includes at least one mark, adapted to indicate a depth of insertion of the support element in the body. For some applications, a distance of the mark from the distal end of the support element is between about 2.5 cm and about 3 cm.

For some applications, the support element includes a stopper, adapted to prevent insertion of the support element into the body beyond a certain depth. For some applications, a distance of the stopper from the distal end of the support element is between about 2.5 cm and about 3 cm.

- 5 For some applications, the support element is bent at one or more locations. For some applications, an angle of a bend of the support element is between about 20 and about 40 degrees. For some applications, a distance of a bend of the support element from the distal end of the support element is between about 2 cm and about 3 cm.

- 10 There is still additionally provided, in accordance with an embodiment of the present invention, apparatus for facilitating delivery of a drug to a subject, including:

an elongated generally rigid support element having a length of at least 1.8 cm, and having a distal end;

- one or more electrodes fixed to the support element in a vicinity of the distal end thereof, and configured to be positioned in a vicinity of a site of the subject when the support element is inserted into a body of the subject, such that a portion of the support element remains outside of the body, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

- a control unit, coupled to the support element, and adapted to:
25 drive the electrodes to apply an electrical current to the site, and
configure the current to induce an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of the drug across the BBB into a central nervous system (CNS) of the subject.

- In an embodiment, the site includes the SPG of the subject, and the electrodes are
30 configured to be positioned in the vicinity of the SPG.

In an embodiment, the support element is substantially straight. For some applications, the support element has a length between about 7 cm and about 13 cm.

For some applications, a portion of the support element adapted for insertion into the body has a length of between about 2.5 cm and about 3 cm.

For some applications, the control unit is adapted to configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

In an embodiment, the support element is adapted to be positioned in the vicinity of the site by insertion through a roof of an oral cavity of the subject. For some applications, the support element is adapted to be positioned in the vicinity of the site by insertion through a greater palatine canal of the subject.

In an embodiment, the support element is adapted to be positioned in the vicinity of the site by insertion through a nose of the subject. For some applications, the support element is adapted to be positioned in the vicinity of the site by insertion through a sphenopalatine foramen of the subject.

For some applications, the support element includes at least one mark, adapted to indicate a depth of insertion of the support element in the body. For some applications, a distance of the mark from the distal end of the support element is between about 2.5 cm and about 3 cm.

For some applications, the support element includes a stopper, adapted to prevent insertion of the support element into the body beyond a certain depth. For some applications, a distance of the stopper from the distal end of the support element is between about 2.5 cm and about 3 cm.

In an embodiment, the support element is bent at one or more locations. For some applications, an angle of a bend of the support element is between about 20 and about 40 degrees. For some applications, a distance of a bend of the support element from the distal end of the support element is between about 2 cm and about 3 cm.

There is still further provided, in accordance with an embodiment of the present invention, apparatus for facilitating a diagnosis of a condition of a subject, including:
an elongated generally rigid support element having a length of at least 1.8 cm, and having a distal end;

one or more electrodes fixed to the support element in a vicinity of the distal end thereof, and configured to be positioned in a vicinity of a site of the subject when the support element is inserted into a body of the subject, such that a portion of the support element remains outside of the body, the site selected from the list consisting of: a
5 sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the
10 subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

a control unit, coupled to the support element, and adapted to:

drive the electrodes to apply an electrical current to the site, and

15 configure the current to induce an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a constituent of a central nervous system (CNS) of the subject across the BBB into a systemic blood circulation of the subject.

In an embodiment, the site includes the SPG of the subject, and the electrodes are configured to be positioned in the vicinity of the SPG.

20 For some applications, the support element is substantially straight.

For some applications, the support element has a length between about 7 cm and about 13 cm. For some applications, a portion of the support element adapted for insertion into the body has a length of between about 2.5 cm and about 3 cm.

For some applications, the control unit is adapted to configure the current to have
25 a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

In an embodiment, the support element is adapted to be positioned in the vicinity
30 of the site by insertion through a roof of an oral cavity of the subject. For some applications, the support element is adapted to be positioned in the vicinity of the site by insertion through a greater palatine canal of the subject.

In an embodiment, the support element is adapted to be positioned in the vicinity of the site by insertion through a nose of the subject. For some applications, the support element is adapted to be positioned in the vicinity of the site by insertion through a sphenopalatine foramen of the subject.

5 In an embodiment, the support element includes at least one mark, adapted to indicate a depth of insertion of the support element in the body. For some applications, a distance of the mark from the distal end of the support element is between about 2.5 cm and about 3 cm.

10 In an embodiment, the support element includes a stopper, adapted to prevent insertion of the support element into the body beyond a certain depth. For some applications, a distance of the stopper from the distal end of the support element is between about 2.5 cm and about 3 cm.

15 For some applications, the support element is bent at one or more locations. For some applications, an angle of a bend of the support element is between about 20 and about 40 degrees. For some applications, a distance of a bend of the support element from the distal end of the support element is between about 2 cm and about 3 cm.

There is also provided, in accordance with an embodiment of the present invention, apparatus for facilitating a diagnosis of a condition of a subject, including:

20 a coil, adapted to be positioned in a vicinity of a site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

25 a control unit, adapted to drive the coil to generate a magnetic field in the vicinity of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a diagnostic agent across the BBB into a
30 central nervous system (CNS) of the subject.

In an embodiment, the site includes the SPG of the subject, and the coil is adapted to be positioned in the vicinity of the SPG.

For some applications, the control unit is adapted to generate the magnetic field with a strength sufficient to stimulate the site, and insufficient to substantially stimulate
5 brain tissue of the subject.

For some applications, the apparatus includes a cooling element, adapted to prevent excessive heating of the coil.

For some applications, the coil includes between about 4 and about 30 loops of wire.

10 In an embodiment, the coil is adapted to be inserted into a nasal cavity of the subject. For some applications, the coil is substantially figure-eight-shaped. Alternatively, the coil is substantially 4-leaf-shaped. Further alternatively, the coil is substantially circular. For some applications, the coil has a diameter of between about 3 mm and about 12 mm.

15 In an embodiment, the coil is adapted to be placed in a vicinity of a temporomandibular joint of the subject. For some applications, the coil has a diameter of between about 3 cm and about 12 cm.

In an embodiment, the coil is adapted to be placed around at least a portion of a head of the subject. For some applications, the coil has a diameter of between about 3
20 cm and about 12 cm.

There is further provided, in accordance with an embodiment of the present invention, apparatus for facilitating delivery of a drug to a subject, including:

a coil, adapted to be positioned in a vicinity of a site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of
25 the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject,
30 and a lesser deep petrosal nerve of the subject; and

a control unit, adapted to drive the coil to generate a magnetic field in the vicinity of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of the drug across the BBB into a central nervous system (CNS) of the subject.

- 5 In an embodiment, the site includes the SPG of the subject, and the coil is adapted to be positioned in the vicinity of the SPG.

For some applications, the control unit is adapted to generate the magnetic field with a strength sufficient to stimulate the site, and insufficient to substantially stimulate brain tissue of the subject.

- 10 For some applications, the apparatus includes a cooling element, adapted to prevent excessive heating of the coil.

For some applications, the coil includes between about 4 and about 30 loops of wire.

- 15 In an embodiment, the coil is adapted to be inserted into a nasal cavity of the subject. For some applications, the coil is substantially figure-eight-shaped. Alternatively, the coil is substantially 4-leaf-shaped. Further alternatively, the coil is substantially circular. For some applications, the coil has a diameter of between about 3 mm and about 12 mm.

- 20 In an embodiment, the coil is adapted to be placed in a vicinity of a temporomandibular joint of the subject. For some applications, the coil has a diameter of between about 3 cm and about 12 cm.

In an embodiment, the coil is adapted to be placed around at least a portion of a head of the subject. For some applications, the coil has a diameter of between about 3 cm and about 12 cm.

- 25 There is still further provided, in accordance with an embodiment of the present invention, apparatus for facilitating a diagnosis of a condition of a subject, including:

- 30 a coil, adapted to be positioned in a vicinity of a site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an

effluent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

- 5 a control unit, adapted to drive the coil to generate a magnetic field in the vicinity of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a constituent of a central nervous system (CNS) of the subject across the BBB into a systemic blood circulation of the subject.

In an embodiment, the site includes the SPG of the subject, and the coil is adapted to be positioned in the vicinity of the SPG.

- 10 For some applications, the control unit is adapted to generate the magnetic field with a strength sufficient to stimulate the site, and insufficient to substantially stimulate brain tissue of the subject.

For some applications, the apparatus includes a cooling element, adapted to prevent excessive heating of the coil.

- 15 For some applications, the coil includes between about 4 and about 30 loops of wire.

- In an embodiment, the coil is adapted to be inserted into a nasal cavity of the subject. For some applications, the coil is substantially figure-eight-shaped. Alternatively, the coil is substantially 4-leaf-shaped. Alternatively, the coil is
20 substantially circular. For some applications, the coil has a diameter of between about 3 mm and about 12 mm.

In an embodiment, the coil is adapted to be placed in a vicinity of a temporomandibular joint of the subject. For some applications, the coil has a diameter of between about 3 cm and about 12 cm.

- 25 In an embodiment, the coil is adapted to be placed around at least a portion of a head of the subject. For some applications, the coil has a diameter of between about 3 cm and about 12 cm.

There is additionally provided, in accordance with an embodiment of the present invention, apparatus for application to a subject, including:

- 30 an elongated support element having a length of between about 1.8 cm and about 4 cm, and having a proximal end and a distal end;

one or more electrodes fixed to the support element in a vicinity of the distal end thereof; and

a control unit, coupled to the support element in a vicinity of the proximal end thereof, and including a battery, the control unit adapted to:

- 5 drive the electrodes to apply an electrical current to tissue of the subject, and
 configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1
10 second and about 2 minutes.

In an embodiment, the tissue is selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic
15 ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject, and the control unit is adapted to drive the electrodes to apply the current to the selected tissue.

20 In an embodiment, the apparatus includes an oral appliance, coupled to the support element, and shaped so as to define a surface that fits closely to a roof of an oral cavity.

For some applications, the support element has a length of between about 1.8 cm and about 3 cm. For some applications, the control unit has a volume, including the
25 battery, of less than about 3 cm³.

For some applications, the control unit is adapted to apply the current having on periods of between about 60 seconds and about 105 seconds, and off periods of between about 30 seconds and 90 seconds. For some applications, the control unit is adapted to apply the current having on periods of about 90 seconds, and off periods of about 60
30 seconds.

There is yet additionally provided, in accordance with an embodiment of the present invention, apparatus for application to a subject, including:

an elongated support element having a length of between about 1.8 cm and about 4 cm, and having a proximal end and a distal end;

5 one or more electrodes fixed to the support element in a vicinity of the distal end thereof;

a receiver, fixed to the support element in a vicinity of the proximal end thereof;

and

a control unit, adapted to be coupled to the receiver, and adapted to:

10 drive the electrodes to apply an electrical current to tissue of the subject, and

configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1

15 second and about 2 minutes.

In an embodiment, the tissue is selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject, and the control unit is adapted to drive the electrodes to apply the current to the selected tissue.

25 For some applications, the support element has a length of between about 1.8 cm and about 3 cm.

For some applications, the receiver includes an electrical contact site, and the control unit is adapted to be coupled to the receiver by being brought into physical contact with the electrical contact site.

30 For some applications, the receiver includes a transducer, and the control unit includes a wireless transmitter, which is adapted to couple the control unit to the receiver via wireless electromagnetic communication with the transducer. For some applications,

the transducer includes a coil. For some applications, the control unit is adapted to be positioned outside of a head of the subject during operation.

For some applications, the control unit is adapted to be positioned inside an oral cavity of the subject. For some applications, the apparatus includes an oral appliance,
5 adapted to be fixed to the control unit, and shaped so as to define a surface that fits closely to a roof of the oral cavity.

For some applications, the receiver has a volume of less than about 0.8 cm^3 . For some applications, the receiver has a volume of less than about 0.15 cm^3 .

For some applications, the control unit is adapted to apply the current having on
10 periods of between about 60 seconds and about 105 seconds, and off periods of between about 30 seconds and 90 seconds. For some applications, the control unit is adapted to apply the current having on periods of about 90 seconds, and off periods of about 60 seconds.

There is also provided, in accordance with an embodiment of the present
15 invention, apparatus for application to a subject, including:

an ENT endoscope, having at least one working channel;

at least one electrode, adapted to be passed through the working channel, and positioned in a vicinity of tissue of the subject; and

a control unit, coupled to the electrode, and adapted to drive the electrode to
20 apply a non-ablating electrical signal to the tissue.

For some applications, the control unit is adapted to configure the signal to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2
25 minutes, and off periods of between about 1 second and about 2 minutes.

In an embodiment, the tissue is selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic
30 ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the

subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject, and the control unit is adapted to drive the electrode to apply the signal to the selected tissue.

5 For some applications, the ENT endoscope includes a side-viewing scope having a viewing angle of between about 30 and about 120 degrees relative to a longitudinal axis of the endoscope. For some applications, the electrode is adapted to be positioned so as to be viewable by the side-viewing scope.

There is further provided, in accordance with an embodiment of the present invention, apparatus for modifying a property of a brain of a subject, including:

10 at least one electrode, adapted to be positioned in a vicinity of a mucous membrane of a palate of an oral cavity of the subject; and

a control unit, adapted to drive the electrode to apply an electrical current to the mucous membrane, and to configure the current to be capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject.

15 For some applications, the control unit is adapted to configure the current to have a magnitude sufficient to activate a sphenopalatine ganglion (SPG) of the subject via nerve fibers in physical contact with the mucous membrane.

For some applications, the control unit is adapted to configure the current to increase the permeability of the BBB to a magnitude sufficient to treat a condition of the
20 subject. Alternatively or additionally, the control unit is adapted to configure the current to increase the permeability of the BBB to a magnitude sufficient to perform a diagnosis of a condition of the subject.

There is still further provided, in accordance with an embodiment of the present invention, apparatus for modifying a property of a brain of a subject, including:

25 at least one electrode, adapted to be positioned in a vicinity of a mucous membrane of a palate of an oral cavity of the subject; and

a control unit, adapted to drive the electrode to apply an electrical current to the mucous membrane, and to configure the current to be capable of inducing an increase in cerebral blood flow (CBF) of the subject.

For some applications, the control unit is adapted to configure the current to have a magnitude sufficient to activate a sphenopalatine ganglion (SPG) of the subject via nerve fibers in physical contact with the mucous membrane.

For some applications, the control unit is adapted to configure the current to
5 increase the CBF to a magnitude sufficient to treat a condition of the subject.

There is still further provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a subject, including:

positioning at least one electrode at at least one site of the subject for less than about 3 hours, the site selected from the list consisting of: a sphenopalatine ganglion
10 (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject,
15 a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject;

applying an electrical current to the site of the subject; and

configuring the current to induce an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a diagnostic agent across
20 the BBB into a central nervous system (CNS) of the subject.

For some applications, positioning the electrode includes:

applying the electrical current to the site;

observing one or more physiological responses of the subject to the current; and

verifying desired placement of the electrode responsive to the observation.

25 There is yet additionally provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a subject, including:

positioning at least one electrode at at least one site of the subject for less than about 3 hours, the site selected from the list consisting of: a sphenopalatine ganglion
30 (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a

maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

5 applying an electrical current to the site of the subject; and

 configuring the current to induce an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a constituent of a central nervous system (CNS) of the subject across the BBB into a systemic blood circulation of

10 the subject.

For some applications, the method includes measuring a concentration of the constituent in the systemic blood circulation.

For some applications, positioning the electrode includes:

15 applying the electrical current to the site;

 observing one or more physiological responses of the subject to the current; and

 verifying desired placement of the electrode responsive to the observation.

There is also provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a subject, including:

20 selecting a site from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater

25 superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject;

 and

 generating a magnetic field in the vicinity of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a diagnostic agent across the BBB into a central nervous system

30 (CNS) of the subject.

There is still further provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a subject, including:

5 selecting a site from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject;
10 and

 generating a magnetic field in the vicinity of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a constituent of a central nervous system (CNS) of the subject across the BBB into a systemic blood circulation of the subject.

15 For some applications, the method includes measuring a concentration of the constituent in the systemic blood circulation.

There is still additionally provided, in accordance with an embodiment of the present invention, a method including:

 inserting an ENT endoscope, having at least one working channel, into a body of
20 a subject;
 passing at least one electrode through the working channel;
 positioning the electrode in a vicinity of tissue of the subject;
 driving the electrode to apply a non-ablating electrical signal to the tissue; and
 performing a diagnostic procedure following initiation of application of the
25 signal.

There is further provided, in accordance with an embodiment of the present invention, a method for modifying a property of a brain of a subject, including:

 applying to a branch of a cranial nerve V of the subject an electrical current configured to affect physiological activity of a sphenopalatine ganglion (SPG) of the
30 subject at a level sufficient to induce an increase in permeability of a blood-brain barrier (BBB) of the subject; and

performing a diagnostic activity with respect to a condition of the subject, in conjunction with the increase in permeability of the BBB.

For some applications, the method includes administering a sedative to the subject in conjunction with applying the current. Alternatively or additionally, the method includes administering an anesthetic to the subject in conjunction with applying the current.

For some applications, applying the current includes placing one or more electrodes on a surface of a face of the subject, and driving the electrodes to apply the current to the branch of the cranial nerve V.

There is also provided, in accordance with an embodiment of the present invention, a method for modifying a property of a brain of a subject, including:

generating a magnetic field in the vicinity of a branch of a cranial nerve V of the subject configured to affect physiological activity of a sphenopalatine ganglion (SPG) of the subject at a level sufficient to induce an increase in permeability of a blood-brain barrier (BBB) of the subject; and

performing a diagnostic activity with respect to a condition of the subject, in conjunction with the increase in permeability of the BBB.

For some applications, the method includes administering a sedative to the subject in conjunction with generating the magnetic field. Alternatively or additionally, the method includes administering an anesthetic to the subject in conjunction with generating the magnetic field.

There is additionally provided, in accordance with an embodiment of the present invention, a method for modifying a property of a brain of a subject, including:

applying an electrical current to a mucous membrane of a palate of an oral cavity of the subject, the current capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject; and

performing a diagnostic activity with respect to a condition of the subject, in conjunction with the increase in permeability of the BBB.

In an embodiment, the method includes administering a sedative to the subject in conjunction with applying the current. Alternatively or additionally, the method

includes administering an anesthetic to the subject in conjunction with applying the current.

For some applications, applying the current includes configuring the current to have a magnitude sufficient to activate a sphenopalatine ganglion (SPG) of the subject
5 via nerve fibers in physical contact with the mucous membrane.

There is also provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a patient, including:

stimulating a modulation target location of the patient at a level sufficient to increase permeability of a blood-brain barrier (BBB) of the patient; and
10 administering a diagnostic agent capable of passing through the BBB and into a central nervous system (CNS) of the patient while the permeability of the BBB is increased.

There is further provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a patient, including:

15 stimulating a modulation target location of the patient at a level sufficient to increase permeability of a blood-brain barrier (BBB) of the patient; and
receiving a constituent of a central nervous system (CNS) of the patient that passes from the CNS and through the BBB while the permeability of the BBB is increased.

20 There is additionally provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a central nervous system (CNS) of a subject, the method including:

stimulating at least one site of the subject by applying an electrical current to the site, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the
25 subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between the anterior ethmoidal nerve and the SPG, a communicating branch between the posterior ethmoidal nerve and the SPG, a nerve of the pterygoid canal of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating
30 branch between a maxillary nerve of the subject and the SPG, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital nerve of the subject, an otic

ganglion of the subject, an afferent fiber going into the otic ganglion, and an efferent fiber going out of the otic ganglion;

configuring the stimulation so as to cause an increase in molecular passage between the CNS and another body compartment of the subject;

- 5 taking a sample from the body compartment;
determining a level of a constituent of the sample; and
interpreting a low value of the level as indicative of an increased likelihood that the subject suffers from the CNS condition.

10 There is yet additionally provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a central nervous system (CNS) of a subject, the method including:

stimulating at least one site of the subject selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between the anterior
15 ethmoidal nerve and the SPG, a communicating branch between the posterior ethmoidal nerve and the SPG, a nerve of the pterygoid canal of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve of the subject and the SPG, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital
20 nerve of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion, and an efferent fiber going out of the otic ganglion;

configuring the stimulation so as to cause an increase in molecular passage between the CNS and another body compartment of the subject;

- 25 taking a sample from the body compartment;
determining a level of a constituent of the sample; and
interpreting a low value of the level as indicative of an increased likelihood that the subject suffers from the CNS condition.

For some applications, stimulating includes applying magnetic stimulation to the site. For some applications, stimulating includes applying electromagnetic stimulation to
30 the site. For some applications, stimulating includes applying chemical stimulation to the site. For some applications, stimulating includes applying mechanical stimulation to the site.

For some applications, the method includes interpreting a high value of the level as indicative of a decreased likelihood that the subject suffers from the CNS condition.

For some applications, the body compartment includes a systemic blood circulation of the subject, and configuring the stimulation includes configuring the stimulation so as to cause the increase in molecular passage between the CNS and the systemic blood circulation. Alternatively or additionally, the body compartment includes plasma of the subject, and configuring the stimulation includes configuring the stimulation so as to cause the increase in molecular passage between the CNS and the plasma. Further alternatively or additionally, the body compartment includes serum of the subject, and configuring the stimulation includes configuring the stimulation so as to cause the increase in molecular passage between the CNS and the serum. Still further alternatively or additionally, the body compartment is ascites of the subject, and configuring the stimulation includes configuring the stimulation so as to cause the increase in molecular passage between the CNS and the ascites.

In an embodiment, the site includes the SPG, and stimulating the site includes stimulating the SPG.

In an embodiment, the CNS condition includes Alzheimer's disease, and interpreting the low value includes interpreting the low value as indicative of the increased likelihood that the subject suffers from Alzheimer's disease. For some applications, the constituent includes amyloid-beta peptide, and determining the level of the constituent includes determining the level of the amyloid-beta peptide. Alternatively or additionally, the constituent includes presenilin-1, and determining the level of the constituent includes determining the level of the presenilin-1.

There is still additionally provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a central nervous system (CNS) of a subject, the method including:

determining a level of a constituent of a sample taken from a body compartment of the subject other than the CNS after commencement of electrical stimulation of at least one site of the subject selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between the anterior ethmoidal nerve and the SPG, a communicating branch between the posterior ethmoidal nerve and

the SPG, a nerve of the pterygoid canal of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve of the subject and the SPG, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital nerve of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion, and an efferent fiber going out of the otic ganglion; and

interpreting a low value of the level as indicative of an increased likelihood that the subject suffers from the CNS condition.

There is still further provided, in accordance with an embodiment of the present invention, a method for facilitating a diagnosis of a condition of a central nervous system (CNS) of a subject, the method including:

determining a level of a constituent of a sample taken from a body compartment of the subject other than the CNS after commencement of stimulation of at least one site of the subject selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between the anterior ethmoidal nerve and the SPG, a communicating branch between the posterior ethmoidal nerve and the SPG, a nerve of the pterygoid canal of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve of the subject and the SPG, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital nerve of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion, and an efferent fiber going out of the otic ganglion; and

interpreting a low value of the level as indicative of an increased likelihood that the subject suffers from the CNS condition.

For some applications, determining the level after the commencement of the stimulation includes determining the level after the commencement of magnetic stimulation of the site. Alternatively or additionally, determining the level after the commencement of the stimulation includes determining the level after the commencement of electromagnetic stimulation of the site. Further alternatively or additionally, determining the level after the commencement of the stimulation includes determining the level after the commencement of chemical stimulation of the site. Still

further alternatively or additionally, determining the level after the commencement of the stimulation includes determining the level after the commencement of mechanical stimulation of the site.

5 For some applications, the body compartment includes a systemic blood circulation of the subject, and determining the level includes determining the level of the constituent of the sample taken from the systemic blood circulation. For some applications, the body compartment includes plasma of the subject, and determining the level includes determining the level of the constituent of the sample taken from the plasma. For some applications, the body compartment includes serum of the subject, and determining the level includes determining the level of the constituent of the sample taken from the serum. For some applications, the body compartment is ascites of the subject, and determining the level includes determining the level of the constituent of the sample taken from the ascites.

15 In an embodiment, the site includes the SPG, and determining the level includes determining the level of the constituent of the sample taken from the body compartment after the commencement of the stimulation of the SPG.

20 In an embodiment, the CNS condition includes Alzheimer's disease, and interpreting the low value includes interpreting the low value as indicative of the increased likelihood that the subject suffers from Alzheimer's disease. For some applications, the constituent includes amyloid-beta peptide, and determining the level of the constituent includes determining the level of the amyloid-beta peptide. For some applications, the constituent includes presenilin-1, and determining the level of the constituent includes determining the level of the presenilin-1.

25 The present invention will be more fully understood from the following detailed description of the embodiments thereof, taken together with the drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A and 1B are schematic pictorial views of an insertable stimulator for stimulation of a modulation target site, in accordance with embodiments of the present invention;

Figs. 2A and 2B are schematic pictorial views of a support element of the stimulator of Figs. 1A and 1B inserted into a human nasal cavity, in accordance with embodiments of the present invention;

5 Fig. 3 is a schematic block diagram illustrating circuitry for use with the stimulator shown in Figs. 1A and 1B, in accordance with an embodiment of the present invention;

Figs. 4A and 4B are schematic illustrations depicting different modes of operation of stimulators such as those shown in Figs. 1A and 1B, in accordance with embodiments of the present invention;

10 Fig. 5 is a schematic illustration of a mode of operation of the stimulators shown in Figs. 1A and 1B, in accordance with an embodiment of the present invention;

Fig. 6 is a schematic block diagram illustrating circuitry for use with the stimulator shown in Figs. 1A and 1B, where the stimulator is driven by an external controller and energy source using a modulator and a demodulator, in accordance with
15 an embodiment of the present invention;

Figs. 7A and 7B are schematic illustrations of nasal magnetic induction devices, in accordance with an embodiment of the present invention;

Figs. 8A and 8B are schematic illustrations of an external magnetic induction device, in accordance with an embodiment of the present invention;

20 Fig. 9 is a schematic illustration of a nasal applicator, in accordance with an embodiment of the present invention;

Fig. 10 is a graph showing *in vivo* experimental results, measured in accordance with an embodiment of the present invention;

25 Fig. 11 is another graph showing *in vivo* experimental results, measured in accordance with an embodiment of the present invention;

Fig. 12 is a schematic illustration of an implantable neural stimulator, in accordance with an embodiment of the present invention;

30 Fig. 13 shows an electrode configuration for use with an electrode support of the stimulator of Figs. 1A and 1B, or with the stimulator of Fig. 12, in accordance with an embodiment of the present invention;

Fig. 14 is a schematic pictorial view of a distal portion of a stimulator for stimulation of a modulation target site, in accordance with an embodiment of the present invention;

Fig. 15 is a schematic pictorial view of a stimulation system for stimulation of a modulation target site, in accordance with an embodiment of the present invention;

Figs. 16A-D, 17A-D, and 18A-D are graphs showing *in vivo* experimental results, measured in accordance with an embodiment of the present invention;

Fig. 19 is a schematic pictorial view of a fully implantable stimulator for stimulation of an MTL, in accordance with an embodiment of the present invention;

Fig. 20 is a schematic pictorial view of another stimulator for stimulation of an MTL, in accordance with an embodiment of the present invention;

Fig. 21 is a schematic block diagram illustrating circuitry for use with the stimulator shown in Fig. 19, in accordance with an embodiment of the present invention;

Fig. 22 is a schematic block diagram illustrating circuitry for use with the stimulator shown in Fig. 20, in accordance with an embodiment of the present invention;

Figs. 23A and 23B are schematic illustrations depicting different modes of operation of stimulators such as those shown in Figs. 19 and 20, in accordance with embodiments of the present invention;

Fig. 24 is a schematic illustration of a mode of operation of the stimulators shown in Figs. 19 and 20, synchronized with a diagnostic agent delivery system, in accordance with an embodiment of the present invention;

Fig. 25 is a schematic block diagram illustrating circuitry for use with the stimulator shown in Fig. 19, where the stimulator is driven by an external controller and energy source using a modulator and a demodulator, in accordance with an embodiment of the present invention;

Fig. 26 depicts sample modulator and demodulator functions for use with the circuitry of Fig. 25, in accordance with an embodiment of the present invention;

Figs. 27, 28A, and 28B are schematic diagrams illustrating further circuitry for use with implantable stimulators, in accordance with respective embodiments of the present invention;

Figs. 29 and 30 are bar graphs showing experimental data collected in accordance with an embodiment of the present invention;

Fig. 31 is a schematic illustration of a sensor for application to a blood vessel, in accordance with an embodiment of the present invention;

5 Fig. 32 is a schematic illustration of an implantable stimulator for stimulation of an MTL, in accordance with an embodiment of the present invention; and

Fig. 33 is a schematic sectional illustration of a nasal inhaler, for use in presenting an odorant to a subject, in accordance with an embodiment of the present invention.

10

DETAILED DESCRIPTION OF THE INVENTION

Figs. 1A and 1B are schematic pictorial views of an electrical stimulator 4, for stimulation of a sphenopalatine ganglion (SPG) system, as defined hereinabove, and/or at least one other appropriate "modulation target site" (MTS), as defined hereinabove, such as an SPG 6 (Figs. 2A and 2B), in accordance with embodiments of the present invention. Electrical stimulator 4 comprises a control handle 7 and, typically, a substantially rigid support element 8. For some embodiments, support element 8 is not rigid. A distal end 9 of support element 8 typically comprises one or more electrodes 10. It is noted that although control handle 7 is shown in Fig. 1A as being of generally the same length as support element 8, for some embodiments, the control handle is considerably shorter. For some applications, electrodes 10 are recessed within support element 8, as shown in the figure, while for other applications the electrodes are flush with the surface of the support element, or protrude therefrom.

Support element 8 typically comprises a mark 11 that indicates the point at which the support element has been sufficiently inserted into a canal of the nasal cavity, as described hereinbelow with reference to Figs. 2A and 2B. Alternatively or additionally, support element 8 comprises a stopper (not shown) in a vicinity of mark 11, that mechanically prevents further insertion of the support element into the canal.

For some applications, such as insertion via the greater palatine canal in the roof of the oral cavity, support element 8 is substantially straight, as shown in Fig. 1A. For these applications, support element 8 typically has a total length L_1 of between about 7

cm and about 13 cm, and the distal portion of the support element that is inserted into the canal typically has a length L_2 of between about 2.5 and about 3 cm, such as about 2.6 cm. For some patients, values of L_1 and/or L_2 outside of this range are used. For other applications, such as insertion via the nose, support element 8 is typically bent at one or more points, such as shown in Fig. 1B. It is noted that for some applications, insertion via the mouth or via the nose may be accomplished via a straight, bent, or jointed support element. For example, support element 8 may be bent at an angle α of between about 20 degrees and about 40 degrees, such as about 30 degrees at a point positioned a distance L_3 of between about 2 cm and about 3 cm from the distal end of the support element.

Reference is now made to Figs. 2A and 2B, which are schematic pictorial views of support element 8 inserted into a human nasal cavity 14, in accordance with embodiments of the present invention. In Fig. 2A, support element 8 is shown inserted into a vicinity of SPG 6 via the roof of the oral cavity, through a greater palatine canal 12. In Fig. 2B, support element 8 is shown inserted into a vicinity of SPG 6 via the nose, through a sphenopalatine foramen canal 13.

Support element 8 and electrodes 10 are typically adapted to be rapidly delivered to a desired point within nasal cavity 14, such as for treatment of an acute and/or emergency medical condition of a subject. Support element 8 and electrodes 10 are typically not adapted to be implanted at the site for long-term, chronic stimulation, but rather to be positioned in place on a short-term basis (e.g., (a) for several seconds or minutes, (b) for less than about three hours, or, (c) for some applications, for less than about three hours per day or for about a week), until completion of the treatment session. As appropriate, the placement process may be facilitated by fluoroscopy, x-ray guidance, standard endoscopy, fine endoscopic surgery (FES) techniques or by any other effective guidance method known in the art, or by combinations of the aforementioned. It is noted, however, that these facilitation techniques are not necessarily utilized, and that in many acute situations, an emergency medical technician is able to rapidly guide support element 8 and electrodes 10 to the target using only basic techniques.

For some applications, the patient's body temperature (see Figs. 4A and 4B) and/or cerebral blood flow (CBF) is measured concurrently with insertion. The CBF may be measured with, for example, a laser Doppler unit positioned at the subject's

forehead or transcranial Doppler measurements. Verification of proper placement of electrodes 10 onto the appropriate neural structure may be performed by activating electrical stimulator 4, and generally simultaneously monitoring CBF. Alternatively or additionally, the dilation of blood vessels near the surface of one or both of the patient's eyes is visually monitored. The onset of such dilation is easily observed, and indicates that the SPG is being stimulated. Further alternatively or additionally, lacrimation and/or nasal discharge are used as an indication of SPG stimulation.

It is to be understood that support element 8 (Figs. 1A and 1B) comprises one or more electrodes 10, e.g., two electrodes, or an array of microelectrodes. For some applications in which support element 8 comprises a metal outer surface, such that the support element can function as an electrode, a single electrode 10 is used, operating in a monopolar mode. Regardless of the total number of electrodes in use, typically only a single or a double electrode extends to SPG 6.

Each of electrodes 10 typically comprises a suitable conductive material, for example, a physiologically-acceptable material such as silver, iridium, platinum, a platinum iridium alloy, titanium, nitinol, or a nickel-chrome alloy. For some applications, one or more of the electrodes have surface areas ranging from about 1 mm² to about 3 mm².

Each electrode is typically insulated with a physiologically-acceptable material such as polyethylene, polyurethane, or a co-polymer of either of these. The electrodes are typically spiral in shape, for better contact, and may have a hook shaped distal end for hooking into or near the SPG. Alternatively or additionally, the electrodes may comprise simple wire electrodes, spring-loaded "crocodile" electrodes, or adhesive probes, as appropriate. Further alternatively or additionally, the electrodes may comprise needle-like elements, similar to standard EMG stimulation electrodes.

In an embodiment of the invention, electrodes 10 comprise a substantially smooth surface, except that the distal end of each such electrode is configured or treated to have a large surface area. For example, the distal tip may be porous platinized. Alternatively or additionally, at least the tips of electrodes 10, and/or support element 8 includes a coating comprising an anti-inflammatory drug, such as beclomethasone sodium phosphate or beclomethasone phosphate. Alternatively, such an anti-inflammatory drug is injected or otherwise applied.

Fig. 3 is a schematic block diagram illustrating circuitry comprising an inserted unit 20 and an external unit 30, for use with stimulator 4 (Fig. 1A), in accordance with an embodiment of the present invention. Inserted unit 20 typically comprises one or more sensing or signal application electrodes 24. External unit 30 typically comprises a microprocessor 32 which receives an external control signal 34 (e.g., from a physician or from the patient), and a feedback signal 36 measured by one or more of electrodes 24. Control signal 34 may include, for example, operational parameters such as a schedule of operation, patient parameters such as the patient's weight, or signal parameters, such as desired frequencies or amplitudes of a signal to be applied to an MTS. If appropriate, control signal 34 can comprise an emergency override signal, entered by the patient or a healthcare provider to terminate stimulation or to modify it in accordance with a predetermined program. Microprocessor 32, in turn, typically (but not necessarily) processes control signal 34 and feedback signal 36 so as to determine one or more parameters of the electric current to be applied through electrodes 24. Responsive to this determination, microprocessor 32 typically generates a stimulation signal 37 having a desired current or voltage to be applied by electrodes 24 to an MTS, such as SPG 6, or other tissue. The configuration of circuitry in units 20 or 30 may determine the intensity, frequency, shape, monophasic or biphasic mode, or DC offset of the signal (e.g., a series of pulses) applied to designated tissue. In an embodiment, control handle 7 comprises the circuitry of external unit 30, and support element 8 comprises the circuitry of inserted unit 20.

Power for microprocessor 32 is typically supplied by a battery 44 or, optionally, another DC power supply. Grounding is provided by battery 44 or a separate ground 46. If appropriate, microprocessor 32 generates a display signal 38 that drives a display block 40 of external unit 30. Typically, but not necessarily, the display is activated to show feedback data received from electrodes 24, or to provide a user interface for the external unit.

For some applications, the waveform applied by one or more of electrodes 10 to designated tissue of an MTS (e.g., the SPG) comprises a waveform with an exponential decay, a ramp up or down, a square wave, a sinusoid, a saw tooth, a DC component, or any other shape known in the art to be suitable for application to tissue. Alternatively or additionally, the waveform comprises one or more bursts of short shaped or square pulses -- each pulse typically less than about 1 ms in duration. Generally, appropriate

waveforms and parameters thereof are determined during an initial test period of electrical stimulator 4. For some applications, the waveform is dynamically updated according to measured physiological parameters, measured during a period in which electrical stimulator 4 is stimulating an MTS, and/or during a non-activation (i.e.,
5 standby) period.

Fig. 4A is a graph schematically illustrating a mode of operation of one or more of the devices shown in Figs. 1-3, in accordance with an embodiment of the present invention. Typically, the effect of the applied stimulation is monitored by means of a temperature transducer at an MTS-affected organ (e.g., the forehead) or elsewhere in the
10 head, e.g., in the nasal cavity. As shown in Fig. 4A for a step (ON/OFF) mode of stimulation, stimulation of an MTS or related tissue is initiated at a time T1, and this is reflected by a measurable rise in temperature (due to increased blood flow). Once the temperature rises to a predetermined or dynamically-varying threshold (e.g., 37 °C), stimulation is terminated (time T2), responsive to which the temperature falls. As
15 appropriate, when the temperature drops to a designated or dynamically-determined point, the stimulation is reinitiated (time T3). Typically, suitable temperatures or other physiological parameters are determined for each patient so as to provide the optimal treatment. If appropriate, control instructions may also be received from the operator, which may be either the patient himself, or a healthcare worker.

20 Fig. 4B is a graph schematically illustrating a mode of operation of one or more of the devices shown in Figs. 1-3, in accordance with another embodiment of the present invention. In this embodiment, the amplitude of the waveform applied to an MTS is varied among a continuous set of values (S1), or a discrete set of values (S2), responsive to the measured temperature, in order to achieve the desired performance. It will be
25 appreciated that other feedback parameters measured in the head (e.g., intraocular pressure, intracranial pressure and/or CBF), as well as measured systemic parameters (e.g., heart rate) and subjective patient inputs may be used in conjunction with or separately from temperature measurements, in order to achieve generally optimal performance of the implanted apparatus.

30 Fig. 5 is a graph schematically illustrating a mode of operation of one or more of the devices shown in Figs. 1-3, in accordance with an embodiment of the present invention. In this embodiment, a diagnostic agent is administered to the patient, e.g.,

intravenously, prior to the initiation of electrical, chemical, magnetic, electromagnetic and/or mechanical stimulation of an MTS at time T1. Advantageously, this prior generation of heightened concentrations of the diagnostic agent in the blood tends to provide relatively rapid transfer of the diagnostic agent across the BBB and into the
5 central nervous system (CNS), without unnecessarily prolonging the enhanced permeability of the BBB while waiting for the blood concentration of the diagnostic agent to reach an appropriate level. Alternatively, for some applications it is desirable to give a single bolus injection of the diagnostic agent shortly before or after initiation of stimulation of an MTS. Typically, combined administration and stimulation schedules
10 are determined by the patient's physician based on the pharmacokinetic properties of each diagnostic agent targeted at the CNS.

Fig. 6 is a schematic block diagram showing circuitry for parasympathetic stimulation, which is particularly useful in combination with the embodiments shown in Figs. 1A and 1B, in accordance with an embodiment of the present invention. An
15 external unit 80 typically comprises a microprocessor 82 that is powered by a battery 84 and/or an AC power source. Microprocessor 82 is grounded through battery 84 or through an optional ground 86.

In a typical mode of operation, an external control signal 88 is input to microprocessor 82, along with a feedback signal 108 from one or more biosensors 106,
20 which are typically disposed in a vicinity of an inserted unit 100 or elsewhere on or in the patient's body. Responsive to signals 88 and 108, microprocessor 82 typically generates a display signal 89 which drives a display 90, as described hereinabove. In addition, microprocessor 82 typically processes external control signal 88 and feedback signal 108, to determine parameters of a stimulation signal 92 which is applied by at
25 least one electrode 104 to an MTS or to other tissue, as appropriate.

Typically, biosensor 106 comprises implantable or external medical apparatus including, for example, one or more of the following:

- a blood flow sensor,
- a temperature sensor,
- 30 • a chemical sensor,
- an ultrasound sensor,

- transcranial Doppler (TCD) apparatus,
- laser-Doppler apparatus,
- a systemic or intracranial blood pressure sensor (e.g., comprising a piezoelectric crystal or capacitive sensor fixed to a major cerebral blood vessel),
- a tissue vitality sensor, e.g., comprising laser Doppler or other optical apparatus for detecting a NAD/NADH ratio in tissue, using optical techniques known in the art for detecting the metabolic state of a tissue,
- a kinetics sensor, comprising, for example, an acceleration, velocity, or level sensor (e.g., a mercury switch), for indicating body dispositions such as a sudden change in body attitude (as in collapsing),
- an electroencephalographic (EEG) sensor comprising EEG electrodes attached to, or implanted in, the patients head, for indicating changes in neurological patterns, such as symptoms of stroke, or
- other monitors of physiological quantities suitable for carrying out the objects of this or other embodiments of the present invention.

Fig. 7A is a schematic illustration of a nasal magnetic induction device 400, in accordance with an embodiment of the present invention. Nasal magnetic induction device 400 generates a magnetic field in the vicinity of an MTS. The magnetic field induces an electric current in the MTS, which temporarily depolarizes neurons therein, thereby electrically stimulating the MTS.

Nasal magnetic induction device 400 typically comprises a wire coil 410 adapted to be insertable into the nasal cavity, and a control unit 412 coupled to the coil. As appropriate, the coil may be compressed during insertion and expand at the target site, or it may be retracted during insertion within a supporting element 414 of device 400, and released when at the target site. Typically, coil 410 has a diameter D of between about 3 mm and about 12 mm, and comprises between about 4 and about 30 loops of wire. The wire typically has a diameter of between about 50 micrometers and about 200 micrometers. Upon activation, the control unit generates a pulsed electric current in the coil. Because of the close proximity of the coil to an MTS, e.g., an SPG, the control unit typically outputs power sufficient to stimulate the SPG but generally insufficient to

substantially stimulate surrounding peripheral or brain tissue. For some applications, the nasal magnetic induction device further comprises a cooling element (e.g., a thermoelectric cooling element, a liquid cooling mechanism, or an air cooling mechanism), which is adapted to prevent excessive heating of the coil.

5 Fig. 7B is a schematic illustration of a nasal magnetic induction device 420, in accordance with an embodiment of the present invention. Nasal magnetic induction device 420 is similar to nasal magnetic induction device 400, described hereinabove with reference to Fig. 7A, except that nasal magnetic induction device 420 comprises a figure-eight-shaped wire coil 430, which may, for example, enhance focusing of the
10 induced field. Alternatively, nasal magnetic induction device 420 comprises a 4-leaf-shaped wire coil, such as described in the above-cited article to Roth BJ et al.

 Figs. 8A and 8B are schematic illustrations of an external magnetic induction device 440, in accordance with an embodiment of the present invention. External magnetic induction device 440 comprises (a) one or more (typically two) magnetic coils
15 450 adapted to be placed in a vicinity of a temporomandibular joint 452 of a subject, in a vicinity of an MTS, e.g., an SPG, and (b) a control unit 454 coupled to the coils. Typically, each coil 450 has a diameter of between about 30 mm and about 120 mm, and comprises between about 4 and about 30 loops of wire.

 In an embodiment of the present invention, an external magnetic induction
20 device comprises a coil adapted to be placed partially or completely around a head of the subject (not necessarily in the configuration shown in Figs. 8A and 8B), and a control unit coupled to the coil. Typically, the coil has a diameter of between about 3 cm and about 12 cm, and comprises between about 4 and about 30 loops of wire. The coil is configured to focus the generated magnetic field on at least one MTS, e.g., the SPG.

25 Fig. 9 is a schematic illustration of a nasal applicator 300, for use in presenting chemicals to a nasal passage of a subject, in accordance with an embodiment of the present invention. In this embodiment, chemical stimulation of the SPG system (defined hereinabove), and/or of at least one other appropriate MTS, is achieved by presenting chemicals, for example in a liquid or gaseous state, to an air passage of the subject, such
30 as a nasal cavity, a throat, a greater palatine canal, or a sphenopalatine foramen. The temporal profile and other quantitative characteristics of such chemical modulation are believed by the present inventors to have a mechanism of action that has a

neuroanatomical basis overlapping with that of the electrical modulation of the MTS. Furthermore, experimental animal evidence collected by the inventors and described in US Provisional Patent Application 60/368,657 to Shalev and Gross entitled, "SPG stimulation," filed March 28, 2002, which is assigned to the assignee of the present invention and is incorporated herein by reference, suggest a correlation between the mechanisms of increasing CBF and increased cerebrovascular permeability. For some applications, chemical-presentation techniques described herein are practiced in combination with techniques described in US Provisional Patent Application 60/376,048, filed April 25, 2002, entitled, "Methods and apparatus for modifying properties of the BBB and cerebral circulation by using the neuroexcitatory and/or neuroinhibitory effects of odorants on nerves in the head," which is assigned to the assignee of the present patent application and is incorporated herein by reference.

Chemicals that may increase or decrease CBF and/or the permeability of the blood-brain barrier (BBB), include, but are not limited to, propionic acid, cyclohexanone, amyl acetate, acetic acid, citric acid, carbon dioxide, sodium chloride, ammonia, menthol, alcohol, nicotine, piperine, gingerol, zingerone, allyl isothiocyanate, cinnamaldehyde, cuminaldehyde, 2-propenyl/2-phenylethyl isothiocyanate, thymol, and eucalyptol. The chemicals reach the appropriate neural structures, excite (or inhibit) the structures, and consequently induce vasodilatation (or vasoconstriction) and/or cerebrovascular permeability changes.

Reference is again made to Fig. 9. In this illustrated embodiment, chemicals are stored in a storage vessel 302, and are delivered to the nasal passage using one or two typically elongated delivery elements 304, which are adapted to reach an upper region of the nasal cavity of the subject, such as in a vicinity of the sphenopalatine foramen or slightly past the sphenopalatine foramen. A distal end of each delivery element 304 is shaped so as to define one or more openings 306, through which the chemicals are released, either omnidirectionally, or in a directed fashion, such as in the direction of the SPG. (The particular configuration of openings 306 on delivery elements 304 is shown by way of illustration and not limitation; other configurations are also suitable.) As appropriate to the particular application, the chemicals may be delivered, for example, in a gaseous state, in a fine spray (e.g., an aerosol spray), or embedded in a viscous or non-viscous liquid matrix. Delivery of the chemicals to the upper region of the nasal cavity,

which is in the vicinity of the SPG, typically facilitates the direct diffusion of the chemicals to the SPG.

Alternatively, for some applications, chemicals are presented to the nasal passage or throat using apparatus known in the art, such as an aqueous spray nasal inhaler, a metered dose nasal inhaler, or an air-dilution olfactometer. Further alternatively, nasal delivery devices are used that are described in: (a) a PCT patent application to Shalev, entitled, "Methods and apparatus for modifying properties of the BBB and cerebral circulation by using the neuroexcitatory and/or neuroinhibitory effects of odorants on nerves in the head," filed April 25, 2003, which is assigned to the assignee of the present patent application and incorporated herein by reference, (b) the above-referenced US Provisional Patent Application 60/376,048, (c) one or more of the above-referenced PCT Publications WO 03/084591, WO 03/020350, WO 03/000310, WO 02/068031, and WO 02/068029 to Djupesland, (d) the above-referenced US Patent Application Publication 2003/0079742 to Giroux, and/or (e) the above-referenced patents and patent applications to Levin. Still further alternatively, chemical stimulation is applied to the SPG system, and/or to at least one other appropriate MTS using a transpalatine applicator inserted via the greater palatine canal (configuration not shown).

In an embodiment of the present invention, stimulation of the MTS is achieved by applying a neuroexcitatory agent to the MTS. Suitable neuroexcitatory agents include, but are not limited to acetylcholine and urocholine. For some applications, the MTS is stimulated by applying a neuroinhibitory agent, such as atropine, hexamethonium, or a local anesthetic (e.g., lidocaine).

In an embodiment of the present invention, stimulation of an MTS is achieved by applying mechanical stimulation to the MTS, e.g., vibration.

In an embodiment of the present invention, an acute and/or emergency medical condition of a subject is treated by stimulating at least one MTS by applying electrical, magnetic, electromagnetic, chemical, and/or mechanical stimulation to the site. Such treatment is typically applied as soon as possible after diagnosis of the condition, such as in an emergency room or at the location of the subject. Such stimulation is typically applied using:

- one or more of the stimulation devices and/or methods described hereinabove;

- techniques described in US Patent Application 10/258,714, filed October 25, 2002, entitled, "Method and apparatus for stimulating the sphenopalatine ganglion to modify properties of the BBB and cerebral blood flow," or the above-referenced PCT Patent Publication WO 01/85094, which are assigned to the assignee of the present application and are incorporated herein by reference;
- techniques described in US Provisional Patent Application 60/426,180, filed November 14, 2002, entitled, "Surgical tools and techniques for stimulation," which is assigned to the assignee of the present application and is incorporated herein by reference;
- techniques described in US Provisional Patent Application 60/426,182, filed November 14, 2002, entitled, "Stimulation circuitry and control of electronic medical device," which is assigned to the assignee of the present application and is incorporated herein by reference; and/or
- techniques known in the art.

In an embodiment of the present invention, an acute brain injury of a subject is treated by applying electrical, magnetic, electromagnetic, chemical, and/or mechanical stimulation to at least one MTS, and configuring the stimulation so as to increase CBF. Such increased CBF increases blood flow to affected brain tissue, which generally causes increased survival of neurons, and thus decreased damage from the injury. Such acute brain injuries include, but are not limited to, ischemic stroke, vasospasm following subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), and seizure.

In an embodiment of the present invention, occlusion within the retinal circulation of a subject is treated by applying electrical, magnetic, electromagnetic, chemical, and/or mechanical stimulation to at least one MTS, and configuring the stimulation so as to induce vasodilation and/or increase retinal blood flow, and thereby treat the condition. For some conditions, increased retinal blood flow releases a block that caused the occlusion. Occlusions of the retinal circulation include retinal artery occlusion (RAO) and retinal venous occlusion (RVO). Optionally, stimulation techniques are used that are described in US Patent Application 10/294,310 to Gross et al., which is assigned to the assignee of the present application and is incorporated herein by reference, such as techniques described with respect to Fig. 14 thereof.

In an embodiment of the present invention, a complication of SAH of a subject is treated by applying electrical, magnetic, electromagnetic, chemical, and/or mechanical stimulation to at least one MTS, and configuring the stimulation so as to dilate cerebral vessels of the subject. The currently-preferred conventional treatment for SAH includes a surgical procedure in which a medical vehicle is used to treat the SAH. The medical vehicle may comprise, for example: (a) a tool for treating the SAH such as by clipping the aneurysm that caused the SAH, and/or (b) a pharmaceutical treatment. However, the presence of blood in the subarachnoid space sometimes causes increased sensitization of large cerebral arteries, resulting at a later time in cerebral vasospasms. These late-onset vasospasms, in turn, cause brain ischemia and often irreversible damage (see the above-referenced article by Van Gijn J et al.). Therefore, the stimulation of the MTS of this embodiment of the present invention is typically applied in conjunction with such a treatment (e.g., before, during or after the treatment), typically to the SPG, in order to counteract the reduced CBF sometimes caused by blood passage into the subarachnoid space. For some applications, the stimulation of the MTS is initiated at a time after the treatment when the hemorrhage has already been substantially reduced (at which time, in the absence of MTS stimulation, CBF is frequently reduced below desired levels). Alternatively, the stimulation of the MTS is initiated prior to this point, but generally has its strongest elevating effect on CBF once the hemorrhage has been substantially reduced. In either case, the MTS is typically configured to generally improve the temporal profile of the cerebral blood flow.

Alternatively or additionally, the MTS stimulation is performed in conjunction with treatments for other medical conditions typically associated with a decrease in CBF, in order to minimize, eliminate, or even reverse the decrease. Such other treatments conditions include stroke and depression (it is believed by some researchers that some occurrences of depression are related to reduced CBF).

The passage of certain molecules from cerebral blood vessels into the brain is hindered by the BBB. The endothelium of the capillaries, the plasma membrane of the blood vessels, and the foot processes of the astrocytes all impede uptake by the brain of the molecules. The BBB generally allows only small molecules (e.g., hydrophilic molecules of molecular weight less than about 200 Da, and lipophilic molecules of less than about 500 Da) to pass from the circulation into the brain.

In an embodiment of the present invention, the short-term MTS stimulation techniques described herein are used in order to facilitate a diagnosis of a condition of the CNS. For some applications, stimulation of the MTS enhances delivery of diagnostic molecules across the BBB by modulation of at least one MTS and/or another
5 parasympathetic center. These techniques typically stimulate the nerve fibers of the MTS, thereby inducing the middle and anterior cerebral arteries to dilate, and also result in increased CNS bioavailability of various compounds. In this manner, the movement of large diagnostic molecules from within blood vessels to the CNS parenchyma is substantially increased.

10 For other applications, short-term stimulation of the MTS enhances clearance of at least one constituent of the CNS, such as a protein, from the CNS, across the BBB, and into the systemic blood circulation of the subject. Once the constituent is in the blood circulation, a conventional blood assay is performed in order to detect the constituent. In the absence of the increased permeability of the BBB caused by the
15 stimulation techniques described herein, these constituents do not generally cross the BBB to the blood circulation in quantities sufficient for accurate detection and diagnosis. The presence of specific proteins in unusually large quantities in the CNS is often an indication of a disorder of the CNS, such as Alzheimer's disease.

For some applications, the diagnostic techniques described herein are practiced
20 in combination with the techniques described in (a) the above-referenced US provisional patent application, filed September 26, 2003, entitled, "Diagnostic applications of stimulation," and/or (b) US Provisional Application 60/388,931, filed June 14, 2002, entitled, "Methods and systems for management of Alzheimer's disease." Both of these applications are assigned to the assignee of the present application and are incorporated
25 herein by reference.

In an embodiment of the present invention, the short-term MTS stimulation techniques described herein are used in order to facilitate delivery of a drug to the CNS. For some applications, stimulation of the MTS enhances delivery of therapeutic molecules across the BBB by modulation of at least one MTS and/or another
30 parasympathetic center. These techniques typically excite the nerve fibers of the MTS, thereby inducing the middle and anterior cerebral arteries to dilate, and also causing the walls of these cerebral arteries to become more permeable to large molecules. In this

manner, the movement of large therapeutic molecules from within blood vessels to tissue of the CNS is substantially increased. For some applications, these techniques are used to facilitate delivery of a drug that is infrequently administered, such as because of peripheral toxicity (e.g., Carmustine (BCNU) is typically administered once every few months).

It is hypothesized that at least two neurotransmitters play an important role in the change in properties of the BBB -- vasoactive intestinal polypeptide (VIP) and nitric oxide (NO). (Acetylcholine may also be involved.) VIP is a short peptide, and NO is a gaseous molecule. VIP is believed to be a major factor in facilitating plasma protein extravasation (PPE), while NO is also considered to be related to vasodilation. For some applications, the parameters of electrical or magnetic stimulation applied to an MTS are varied, as appropriate, in order to selectively influence the activity of one or both of these neurotransmitters. For example, stimulation of the parasympathetic nerve at different frequencies can induce differential secretion -- low frequencies cause secretion of NO, while high frequencies (e.g., above about 10 Hz) cause secretion of peptides (VIP).

For other applications of electrical stimulation (in this case, inhibition), a constant level DC signal, or a slowly varying voltage ramp is applied, in order to block parasympathetic neural activity in affected tissue. Alternatively, similar results can be obtained by electrically stimulating at a rate higher than about 10 Hz, because this tends to exhaust neurotransmitters. Thus, the stimulation may be configured to induce parasympathetic electrical block, in order to cause vasoconstriction by mimicking the overall effect of chemical block on the MTS. Conditions treatable in this manner include headaches, e.g., cluster headaches or migraine headaches, and multiple sclerosis.

In an embodiment of the present invention, acute conditions are treated by applying bipolar stimulation, in which a first electrode is applied to a first MTS, and a second electrode is applied to a second MTS.

In an embodiment of the present invention, a medical condition of a subject, such as an acute and/or emergency condition, is treated by electrically stimulating at least one MTS using one or more of the following stimulation parameters:

- The total duration of stimulation is between about 0.25 and about 4 hours, such as about 3 hours.

- Stimulation is applied with a duty cycle (intermittency) of about 5 minutes "active stimulation," and about 10 minutes "withholding from stimulation." (The active stimulation period is typically between about 2 and about 10 minutes, while the withholding from stimulation period is typically between about 5 and about 15 minutes.)
- During the active stimulation period, stimulation is applied for an "on" period of about 90 seconds of each successive about 150-second period within the active stimulation period, and, thereafter, not applied during an "off" period, for about 60 seconds of the 150-second period. (Alternatively, instead of a 150-second period, the period may be between about 50 and 150 seconds, with the stimulation being applied for between about 30% and about 70% thereof.)
- During the "on" periods, stimulation is applied as repeated DC pulses having a pulse width of about 1 ms, each typically followed by a duration of sufficient length to enable repolarization of nerve tissue of the MTS, e.g., about 99 ms. These example values represent an effective 10 Hz signal. Other suitable values range from about 2 Hz to about 50 Hz.
- Each DC pulse typically has a magnitude less than about 8 V, such as between about 1 and about 7 V, for example, about 3.5 V. The current of the pulse is between about 0.2 and about 10 mA, such as between about 0.5 and about 5 mA, for example, between about 1 and about 2 mA.

In an embodiment of the present invention, an SPG of the subject is indirectly activated by stimulating a branch of cranial nerve V of the subject, including, for example, afferent fibers of the cranial nerve V, either electrically, magnetically, or electromagnetically. A reflex response to such stimulation leads to activation of the SPG. Such stimulation increases permeability of the BBB, and/or increases CBF. Typically, the stimulation is performed while the subject is under general anesthesia or sedation. For some applications, cranial nerve V is stimulated by non-invasively attaching electrodes to the surface of the face of the subject, typically using techniques commonly used for transcutaneous electrical nerve stimulation (TENS).

Reference is now made to Fig. 10, which is a graph showing *in vivo* experimental results, measured in accordance with an embodiment of the present invention. Two pigs were anesthetized using 1 g pentobarbital, and anesthesia was maintained using inhaled isoflurane under spontaneous breathing. The oral mucosa in the greater palatine canal was exposed, and a bipolar concentric electrode was inserted into the canal and connected to a controller. The SPG was stimulated for two hours using the following signal parameters: a 90 second/60 second on/off pattern, 10 Hz, 1 ms pulse width, and varying voltage up to 8 V. During the first hour of stimulation, 400 mg of the fluorescent fluid-phase marker fluorescein isothiocyanate-labeled 40 kDa dextran (FITC dextran) was administered in 500 ml normal saline solution. A third pig, in which an electrode was not implanted, served as a control, and also received 400 mg FITC dextran. The pigs were sacrificed an hour after the end of the stimulation. No perfusion was performed.

Fig. 10 shows the brain uptake index (BUI) of the FITC dextran conjugate in several locations of the brain of each of the three pigs. BUI is the ratio of the brain tissue concentration of the FITC dextran conjugate to the body weight-normalized dosage (i.e., [brain tissue concentration] / [total dosage/body weight]). As can be seen in the figure, uptake of the FITC dextran conjugate was substantially greater in all of the shown brain regions of both experimental pigs than in the corresponding regions of the control pig. These results demonstrate that SPG stimulation of the experimental pigs substantially increased the BBB permeability of these pigs to the FITC dextran conjugate compared to the BBB permeability of the control pig.

Reference is now made to Fig. 11, which is a graph showing *in vivo* experimental results, measured in accordance with an embodiment of the present invention. Eight beagle dogs (body weight of 10-14 kg) were divided into an experimental group (five dogs) and a control group (three dogs). The dogs were anesthetized with 30 mg/kg pentobarbital. A bipolar concentric stimulating electrode was inserted into the right SPG of each dog, by excising the zygomatic arch and underlying muscles in order to reach the sphenopalatine fossa. Correct placement of the stimulation electrode was confirmed by performing a three-minute stimulation session, after which cholinergic indications (lacrimation and nasal discharge) were used as positive indications of proper electrode placement.

An additional setup procedure was performed to verify that the electrodes were properly positioned to activate SPG cerebrovascular efferents fibers. A 2 ml aliquot of iopamidol was autoinjected (Angiomat 6000, Liebel-Flarsheim Co., Ohio, USA) into the right vertebral artery, after which five consecutive angiographic images of the circle of Willis were taken each 200 ms, using a digital subtraction angiography system (DFA-3-30, Hitachi Medical Co., Tokyo, Japan). Subsequently, 15 seconds of SPG stimulation was performed, having the following signal parameters: 10 Hz, 6 V, pulse width of 1 ms, monophasic, and square wave. Seven seconds after commencement of stimulation, i.e., during the stimulation, the angiographic sequence was repeated. After 5 minutes, another angiographic sequence was performed without SPG stimulation. At each step, dimensions of the middle cerebral artery (MCA) and posterior communicating artery (PCOM) were recorded for later analysis of vasodilatation. This setup procedure confirmed proper electrode placement by observation of nasal discharge and ipsilateral lacrimation.

SPG stimulation was applied to the dogs of the experimental group, using the signal parameters used during the setup procedure. During the first 30 minutes following commencement of SPG stimulation, the dogs of the experimental group were continuously administered 190 mg of 10 kDa FITC dextran, intra-aortically via a transfemoral catheter, using a programmed syringe pump. Angiographic imaging was performed at 5, 15, and 25 minutes following commencement of SPG stimulation, and blood samples were collected at 10, 20, 30, and 40 minutes following commencement of SPG stimulation. The dogs of the control group, while not receiving SPG stimulation, were also administered 190 mg FITC dextran for 20 minutes.

At the conclusion of the experiment, the cephalic circulation of the experimental and control dogs was perfused using heparinized saline, through the aortic catheter, in conjunction with bilateral irrigation through both common carotid arteries. Five minutes following commencement of cephalic perfusion, each dog was sacrificed, and the perfusion was continued for an additional 15 minutes. The brain was removed, and biopsies were taken from the following regions: frontal cortex, temporal cortex, frontal white matter, olfactory bulb, striatum, hippocampus, pons, and the temporal muscle. Each tissue sample was homogenized in heparinized saline. The temporal muscle was also collected to serve as non-cerebral control tissue.

Fig. 11 shows the fractional FITC dextran content in several locations of the brain, ipsilateral to stimulation, in dogs of the experimental and control groups. As can be seen in the graph, the uptake of the FITC dextran conjugate was substantially greater in six of the shown brain regions of the stimulated dogs than in the corresponding regions of the control dogs: the frontal cortex, the temporal cortex, the frontal white matter, the olfactory bulb, the striatum, and the hippocampus. These brain regions are protected by the BBB.

In one control measurement shown in Fig. 11, the FITC dextran content was also measured in the pons, which is protected by the BBB but innervated by the otic ganglion rather than by the SPG. The graph shows that SPG stimulation did not increase uptake of the FITC dextran conjugate in the pons. (The vertical lines extending from the top of the bars represent standard deviation.) In another control measurement shown in Fig. 11, the FITC dextran content was also measured in the temporal muscle, which is not protected by the BBB. The graph shows that uptake in the temporal muscle was high and substantially equivalent with and without SPG stimulation. These results demonstrate that, regardless of the presence or absence of SPG stimulation, tissue that is not protected by the BBB shows a substantial increase in the measured quantity of the FITC dextran conjugate.

In addition, the effect of SPG stimulation on vasodilation of the MCA and PCOM was evaluated. The diameters of these arteries were on average 16.1% greater post-stimulation vs. pre-stimulation (with a standard deviation of 8.2%). These results demonstrate that SPG stimulation substantially increased vasodilation of these arteries.

Fig. 12 is a schematic illustration of an implantable neural stimulator 350, in accordance with an embodiment of the present invention. Stimulator 350 comprises an electrode support 352, a receiver 354, and a connecting element 356, such as a connecting tube. (Other suitable structures for connecting element 356 will be apparent to one of ordinary skill in the art, having read the disclosure of the present patent application.) Electrode support 352 comprises one or more electrodes 358, positioned on an electrode surface 360 of the support, such that the electrodes are in contact with a target site (e.g., the SPG) when stimulator 350 is implanted. For some applications, electrodes 358 are arranged in the electrode configuration described hereinbelow with reference to Fig. 13. Receiver 354 receives power and control signals from a control

unit and utilizes the power and control signals to drive current through electrodes 358. Optionally, connecting element 356 comprises one or more marks 362 that indicate the depth of insertion of stimulator 350 into an implantation site of the subject.

Fig. 13 shows an electrode configuration for use, for example, with electrical stimulator 4 of Figs. 1A and 1B, in accordance with an embodiment of the present invention. In this configuration, distal end 9 of support element 8 of electrical stimulator 4 comprises an electrode support 400. Electrode support 400 comprises two insulated regions (i.e., regions having high electrical impedance): an insulated shaft region 410 and an insulated tip region 412. Electrodes 10 of electrical stimulator 4 comprise at least one bipolar electrode 414, comprising an annular electrode 416 and a rod electrode 418, electrically isolated from one another by insulated tip region 412. Alternatively, this configuration is used with stimulator 350 of Fig. 12, in which case electrode support 352 thereof comprises electrode support 400, and electrodes 358 comprise bipolar electrode 414.

Fig. 14 a schematic pictorial view of a distal portion of a stimulator 430, for stimulation of a sphenopalatine ganglion (SPG) system, as defined hereinabove, and/or at least one other appropriate "modulation target site" (MTS), as defined hereinabove, such as an SPG 6 (Figs. 2A and 2B), in accordance with an embodiment of the present invention. Stimulator 430 comprises a semi-flexible catheter 440. A distal tip 442 of the catheter is shaped so as to define at least one opening 444. Stimulator 430 is adapted to apply a chemical substance through opening 444 to at least a portion of the SPG system, and/or to at least one MTS. Stimulator 430 is typically adapted for insertion via a transpalatine or a nasal approach to a vicinity of the SPG system or MTS.

Chemical substances that may stimulate the SPG system or an MTS include, but are not limited to, propionic acid, cyclohexanone, amyl acetate, acetic acid, citric acid, carbon dioxide, sodium chloride, ammonia, menthol, alcohol, nicotine, piperine, gingerol, zingerone, allyl isothiocyanate, cinnamaldehyde, cuminaldehyde, 2-propenyl/2-phenylethyl isothiocyanate, thymol, eucalyptol, a neuroexcitatory agent, such as acetylcholine or urecholine, and a neuroinhibitory agent, such as atropine, hexamethonium, or a local anesthetic (e.g., lidocaine). Alternatively or additionally, the chemical substance includes one or more substances described in one or more of the above-mentioned patents or patent application publications to Levin.

In an embodiment of the present invention, stimulator 430 additionally comprises at least one electrode 445, such as a bipolar electrode 446. Bipolar electrode 446 may, for example, comprise an annular electrode 448 and a rod electrode 450, electrically isolated from one another by an insulated tip region 452. Alternatively, electrode 445 is
5 monopolar, and a ground, such as a ground patch, is placed elsewhere on or in the subject's body, such as on the face. For some applications, electrode 445 is recessed within catheter 440 or is flush with a surface of the catheter (configurations not shown).

For some applications, electrode 446 is activated in order to confirm accurate placement of distal tip 442 in the vicinity of the desired MTS or SPG system. After
10 distal tip 442 has been inserted and initially positioned, electrode 446 is activated to apply an excitatory signal. Observation of an expected physiological response serves to confirm accurate placement. Typical physiological responses to excitation of an MTS or SPG system include, but are not limited to, increased lacrimation, increased nasal discharge, paresthesia (e.g., of the upper palate), or pain. If necessary, distal tip 442 is
15 repositioned and this placement confirmation technique is repeated. After accurate placement has been confirmed, stimulator 430 applies the chemical substance. This technique for confirming placement may be useful, for example, when the chemical substance includes a neuroinhibitory agent, which would not itself induce the observed physiological response. It should be noted that, for these applications, the applied
20 excitatory electrical signal typically does not provide a direct therapeutic benefit. (For other applications, however, the applied excitatory electrical signal may be applied in order to derive a direct therapeutic benefit.)

Alternatively or additionally, after distal tip 442 is inserted and initially positioned, stimulator 430 applies a neuroexcitatory agent, and observation of an
25 expected physiological response serves to confirm accurate placement. After accurate placement has been confirmed, stimulator 430 applies a neuroinhibitory agent to achieve, for example, a direct therapeutic benefit (e.g., treatment of pain). For this application, a separate lumen and/or opening (not shown) may be used for the neuroexcitatory and neuroinhibitory agents, or a common lumen and/or opening may be
30 used. Alternatively, after accurate placement has been confirmed, stimulator 430 applies an excitatory agent to achieve, for example, a direct therapeutic benefit (e.g., increased BBB permeability or cerebral blood flow).

Alternatively or additionally, after distal tip 442 is inserted and initially positioned, stimulator 430 applies an excitatory electrical signal, and observation of an expected physiological response serves to confirm accurate placement. After accurate placement has been confirmed, stimulator 430 applies an inhibitory electrical signal, and
5 configures to the signal to treat a condition of the subject.

Fig. 15 a schematic pictorial view of a stimulation system 500, for stimulation of a sphenopalatine ganglion (SPG) system, as defined hereinabove, and/or at least one other appropriate "modulation target site" (MTS), as defined hereinabove, such as an SPG 6 (Figs. 2A and 2B), in accordance with an embodiment of the present invention.
10 Stimulation system 500 comprises a support element 510, which typically, but not necessarily, is generally rigid (i.e., it generally keeps its original shape during a placement procedure). A distal end 512 of support element 510 comprises one or more electrodes 514. For some applications, electrodes 514 are recessed within support element 510, as shown in the figure, while for other applications the electrodes are flush
15 with the surface of the support element, or protrude therefrom. Alternatively, the electrodes are configured as shown in Figs. 13 and 14.

Support element 510 is adapted to be inserted into a vicinity of an MTS or an SPG system of the subject, via a greater palatine canal in a roof of an oral cavity of the subject. Typically, support element 510 is substantially straight. Support element 510
20 typically comprises one or more marks 516 that indicate the point at which the support element has been sufficiently inserted into the greater palatine canal. Alternatively or additionally, support element 510 comprises a stopper (not shown) in a vicinity of marks 516, that mechanically prevents further insertion of the support element into the canal.

Stimulation system 500 further comprises a semi-flexible oral appliance 518,
25 which is physically coupled to support element 510 by flexible leads 520. Oral appliance 518 comprises a neurostimulator 522, which is electrically coupled to electrodes 514 via leads 520. An upper surface 524 of oral appliance 518 is shaped to fit closely to the roof of the oral cavity, and is adapted to be coupled thereto. For example, oral appliance 518 may be shaped generally similarly to an orthodontic retainer.
30 Neurostimulator 522 is typically battery-powered, and configurable to drive electrodes 514 to stimulate the MTS or SPG system. For some applications, the subject himself

activates neurostimulator 522. Stimulation system 500 is typically adapted to remain in the oral cavity for between several hours and about two days.

In an embodiment of the present invention, a stimulation system for application to a subject comprises an elongated support element having a length of between about 1.8 cm and about 4 cm, such as a length of between about 1.8 cm and about 3 cm. The support element comprises one or more electrodes fixed thereto in a vicinity of a distal end thereof. The stimulation system further comprises a control unit, coupled to the support element in a vicinity of a proximal end thereof. The control unit typically comprises a battery, and is adapted to drive the electrodes to apply an electrical current to tissue of the subject, such as the SPG system and/or at least one MTS. The control unit typically configures the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes. (Together, the on and off periods define a duty cycle.) For example, the control unit may drive the electrodes to apply the current having on periods of between about 60 seconds and about 105 seconds, and off periods of between about 30 seconds and 90 seconds, e.g., on periods of about 90 seconds, and off periods of about 60 seconds.

For some applications, the support element is semi-rigid. For example, the support element and the electrodes together may be similar to conventional concentric needle electrodes, such as Medtronic, Inc. needle electrode model DCN50, or Oxford Instruments Plc. needle electrode models X53153, X53155, X53156, X53158, or X53159.

For some applications, the stimulation system comprises an oral appliance, coupled to the support element, and shaped so as to define a surface that fits closely to a roof of an oral cavity. For example, the oral appliance may be similar to oral appliance 518, described hereinabove with reference to Fig. 15. For some applications, the control unit has a volume, including the battery, of less than about 3 cm³.

In an embodiment of the present invention, a stimulation system for application to a subject comprises an elongated support element having a length of between about 1.8 cm and about 4 cm, such as a length of between about 1.8 cm and about 3 cm. The

support element comprises one or more electrodes fixed thereto in a vicinity of a distal end thereof, and a receiver, fixed to the support element in a vicinity of the proximal end thereof. The stimulation system further comprises a control unit, adapted to be coupled to the receiver. The control unit is adapted to drive the electrodes via the receiver to
5 apply an electrical current to tissue of the subject, such as the SPG system and/or at least one MTS. The control unit typically configures the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods
10 of between about 1 second and about 2 minutes. (Together, the on and off periods define a duty cycle.) For example, the control unit may drive the electrodes to apply the current having on periods of between about 60 seconds and about 105 seconds, and off periods of between about 30 seconds and 90 seconds, e.g., on periods of about 90 seconds, and off periods of about 60 seconds.

15 For some applications, the receiver comprises an electrical contact site, and the control unit is adapted to be coupled to the receiver by being brought into physical contact with the electrical contact site. For example, the control unit may be brought into physical contact by positioning the control unit inside an oral cavity of the subject. For some applications, the stimulation system comprises an oral appliance, adapted to be
20 fixed to the control unit, and shaped so as to define a surface that fits closely to a roof of an oral cavity. For example, the oral appliance may be similar to oral appliance 518, described hereinabove with reference to Fig. 15.

Alternatively, the receiver comprises a transducer, and the control unit comprises a wireless transmitter, which is adapted to couple the control unit to the receiver via
25 wireless electromagnetic communication with the transducer. Typically, the transducer comprises a coil. For some applications, the control unit is adapted to be positioned outside of a head of the subject. Alternatively, the control unit is adapted to be placed in the oral cavity, such as by being fixed to an oral appliance. For some applications, the receiver has a volume of less than about 0.8 cm^3 , such as less than about 0.15 cm^3 .

30 In an embodiment of the present invention, a stimulation system for application to a subject comprises an ENT endoscope, having at least one working channel, and at least one electrode, adapted to be passed through the working channel, and positioned in

a vicinity of tissue of the subject, such as the SPG system and/or at least one MTS. The stimulation system further comprises a control unit, coupled to the electrode, and adapted to drive the electrode to apply a non-ablating electrical signal to the tissue. For some applications, the control unit is adapted to configure the signal to have a pulse
5 frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

For some applications, the ENT endoscope comprises a side-viewing scope
10 having a viewing angle of between about 30 and about 120 degrees relative to a longitudinal axis of the endoscope. Typically, the electrode is adapted to be positioned so as to be viewable by the side-viewing scope.

Reference is now made to Figs. 16A-D, 17A-D, and 18A-D, which are graphs showing *in vivo* experimental results, measured in accordance with an embodiment of
15 the present invention. Baseline angiography was performed on six dogs. Subarachnoid hemorrhage (SAH) was simulated in all six dogs by injection of autologous blood into the cisterna magna. Two days later, the subarachnoid blood injection was repeated. Seven days later, angiography was repeated and the left SPG was exposed microscopically. Angiography was repeated 15 minutes after exposure of the SPG. A
20 bipolar electrode was directly attached to the SPG. The left SPG was then electrically stimulated three times (labeled the first, second, and third stimulations in the figures), and angiography was repeated during each stimulation, 15 minutes after the third stimulation, and 30 minutes after the third stimulation. Forty minutes after cessation of the third stimulation, the left SPG was electrically stimulated three additional times
25 (labeled the fourth, fifth, and sixth stimulations in the figures), and angiography was repeated during each stimulation, 15 minutes after the sixth stimulation, and 30 minutes after the sixth stimulation. All stimulation was performed using the following parameters: 6 V, 10 Hz, and, in alternation, on periods of 90 seconds and off periods of 60 seconds. Adequacy of stimulation was confirmed by the presence of immediate
30 ipsilateral nasal mucous production. Qualitative assessment of the distal intracranial vasculature was also performed.

Comparisons of diameters on day 0, prior to induction of SAH, and on day 7 before SPG exposure ($n = 4-6$ per measurement) showed significant reduction in diameter of the right and left middle cerebral arteries on day 7 compared to day 0 ($22 \pm 11\%$ and $18 \pm 14\%$, respectively, $P < 0.05$, paired t-tests, all values are given as means \pm standard deviation). Comparisons before and after SPG exposure on day 7 showed that there were no significant effects of exposure of the SPG on arterial diameters. Sham stimulation produced no substantial changes in arterial diameters compared to the diameters before stimulation and after SPG exposure ($n = 2$ per measure, paired t-tests).

Reference is again made to Figs. 16A-D, which show the measured diameters of the left (stimulation side) external carotid artery, intracranial internal carotid artery, middle cerebral artery, and anterior cerebral artery, respectively, of five of the dogs at several measurement points in time. (The sixth dog was used for calibration.) These results demonstrate that for the first series of stimulations (first, second, and third stimulations) there were marked increases in the diameters of the intracranial internal carotid, middle cerebral, and anterior cerebral arteries on the stimulation side (left) during stimulation. However, these increases were not statistically significant (ANOVA). For the second series of stimulations (fourth, fifth, and sixth stimulations), there was significant variance in the diameter of the left extracranial and intracranial internal carotid arteries ($P < 0.05$, ANOVA) with pairwise differences between the maximal dilations during stimulation and the value 30 minutes after stimulation.

Reference is again made to Figs. 17A-D, which show the measured diameters of the right (non-stimulation side) external carotid artery, intracranial internal carotid artery, middle cerebral artery, and anterior cerebral artery, respectively, of five of the dogs at several measurement points in time. As can be seen, stimulation of the left SPG had no substantial effect on the diameters of any of these right cerebral arteries.

In a further analysis of the experimental data, the two series of stimulations were combined (i.e., the first together with the fourth stimulations, the second together with the fifth stimulations, the third together with the sixth stimulations, the 15 minutes after the third stimulation together with the 15 minutes after the sixth stimulation, and the 30 minutes after the third stimulation together with the 30 minutes after the sixth stimulation). The combined data were analyzed over time. There was significant variance in diameters for the left extracranial internal carotid artery ($P < 0.05$, ANOVA)

with a significant pairwise difference between the maximal dilation and the diameter 30 minutes after stimulation. This variance was due to dilation, as well as in part to a trend for the diameter to be smaller 30 minutes after stimulation than it was before stimulation. For the left intracranial internal carotid there was significant variance ($P < 0.001$, ANOVA) with pairwise differences between two of the series of stimulations and the diameter before and 30 minutes after stimulation. There were no significant effects of stimulation on the diameters of the left (stimulation side) middle and anterior cerebral arteries, or on any of the right (non-stimulation side) arteries at any time.

Reference is again made to Figs. 18A-D, which show percentage changes from baseline of the diameters of the left (stimulation side) and right (non-stimulation side) external carotid artery, intracranial internal carotid artery, middle cerebral artery, and anterior cerebral artery, respectively, of five of the dogs in combination, at several measurement points in time. Vertical lines on data points indicate standard deviation. Comparisons were made between the right and left arteries at each time by paired t-tests for each separate series of stimulations and for the combined series of stimulations. At baseline on day 0, prior to induction of SAH, and on day 7 after SPG exposure, there were no significant differences between the right and left arteries. There were significant differences between the right and left arteries during the third, fourth, fifth and sixth stimulations for the intracranial internal carotid artery ($P = 0.007, 0.039, 0.01, 0.01$, respectively), during the fourth stimulation for the anterior cerebral artery ($P = 0.05$), and during the sixth stimulation for the extracranial internal carotid artery ($P = 0.047$).

In a further analysis of the experimental data, the two series of stimulations were combined, as described above. Significant differences were found for: (a) the anterior cerebral artery during the first combined stimulation ($P = 0.05$); (b) the extracranial internal carotid ($P = 0.005$), intracranial internal carotid ($P < 0.001$), and middle cerebral arteries ($P = 0.043$) during the second combined stimulation; and (c) the extra- and intracranial internal carotid during the third combined stimulation ($P = 0.009$ and < 0.001 , respectively). Finally, qualitative comparison of the distal vasculature showed marked dilation of the distal vasculature in response to stimulation.

Taken as a whole, these experimental data indicate that SPG stimulation, using the techniques described herein, reverses mild to moderate vasospasm after SAH in dogs.

Fig. 19 is a schematic pictorial view of a fully-implantable stimulator 554, for stimulation of a "modulation target location" (MTL), as defined hereinbelow, such as a sphenopalatine ganglion (SPG) 6, in accordance with an embodiment of the present invention. In Fig. 19, a human nasal cavity 2 is shown, and stimulator 554 is implanted between the hard palate and the mucoperiosteum (not shown) of the roof of the mouth. Branches of parasympathetic neurons coming from SPG 6 extend to the middle cerebral and anterior cerebral arteries (not shown). Preferably, one or more relatively short electrodes 557 extend from stimulator 554 to contact or to be in a vicinity of an MTL, such as SPG 6.

In the present patent application, a "modulation target location" consists of:

- a sphenopalatine ganglion (SPG) (also called a pterygopalatine ganglion);
- an anterior ethmoidal nerve;
- a posterior ethmoidal nerve;
- a communicating branch between the anterior ethmoidal nerve and the SPG (retro-orbital branch);
- a communicating branch between the posterior ethmoidal nerve and the SPG (retro-orbital branch);
- a nerve of the pterygoid canal (also called a vidian nerve), such as a greater superficial petrosal nerve (a preganglionic parasympathetic nerve) or a lesser deep petrosal nerve (a postganglionic sympathetic nerve);
- a greater palatine nerve;
- a lesser palatine nerve;
- a sphenopalatine nerve;

- a communicating branch between the maxillary nerve and the sphenopalatine ganglion;
- a nasopalatine nerve;
- a posterior nasal nerve;
- 5 • an infraorbital nerve;
- an otic ganglion;
- an afferent fiber going into the otic ganglion; and/or
- an efferent fiber going out of the otic ganglion.

For some applications, stimulator 554 is implanted on top of the bony palate, in
10 the bottom of the nasal cavity. Alternatively or additionally, the stimulator is implanted
at the lower side of the bony palate, at the top of the oral cavity. In this instance, one or
more flexible electrodes 557 originating in the stimulator are passed through the palatine
bone or posterior to the soft palate, so as to be in a position to stimulate the SPG or
another MTL. Further alternatively or additionally, the stimulator may be directly
15 attached to the SPG and/or to another MTL.

For some applications, stimulator 554 is delivered to a desired point within nasal
cavity 2 by removably attaching stimulator 554 to the distal end of a rigid or slightly
flexible introducer rod (not shown) and inserting the rod into one of the patient's nasal
passages until the stimulator is properly positioned. As appropriate, the placement
20 process may be facilitated by fluoroscopy, x-ray guidance, fine endoscopic surgery
(FES) techniques or by any other effective guidance method known in the art, or by
combinations of the aforementioned. Preferably, the ambient temperature and/or
cerebral blood flow is measured concurrently with insertion. The cerebral blood flow
may be measured with, for example, a laser Doppler unit positioned at the patient's
25 forehead or transcranial Doppler measurements. Verification of proper implantation of
the electrodes onto the appropriate neural structure may be performed by activating the
device, and generally simultaneously monitoring cerebral blood flow.

The placement process may be performed using techniques described in US
Provisional Patent Application 60/426,180 filed November 14, 2002, entitled, "Surgical

tools and techniques for stimulation," which is assigned to the assignee of the present patent application and is incorporated herein by reference.

The passage of certain molecules from cerebral blood vessels into the brain is hindered by the BBB. The endothelium of the capillaries, the plasma membrane of the blood vessels, and the foot processes of the astrocytes all impede uptake by the brain of the molecules. The BBB generally allows only small molecules (e.g., hydrophilic molecules of molecular weight less than about 200 Da, and lipophilic molecules of less than about 500 Da) to pass from the circulation into the brain.

In accordance with an embodiment of the present invention, parasympathetic activation induced by current from stimulator 554 overcomes the resistance to trans-
BBB molecular movement generated by the endothelium of the cerebral capillaries and the plasma membrane. For some applications, therefore, stimulator 554 may be used to transiently remove a substantial obstacle to the passage of diagnostic agents from the systemic blood circulation to the CNS, and/or of biochemical agents from the CNS to the systemic blood circulation.

It is hypothesized that two neurotransmitters play an important role in this change in properties of the BBB -- vasoactive intestinal polypeptide (VIP) and nitric oxide (NO). (Acetylcholine may also be involved.) VIP is a short peptide, and NO is a gaseous molecule. VIP is believed to be a major factor in facilitating plasma protein extravasation (PPE), while NO is responsible for vasodilation. For some applications, stimulator 554 is adapted to vary parameters of the current applied to an MTL, as appropriate, in order to selectively influence the activity of one or both of these neurotransmitters. For example, stimulation of the parasympathetic nerve at different frequencies can induce differential secretion -- low frequencies cause secretion of NO, while high frequencies (e.g., above about 10 Hz) cause secretion of peptides (VIP).

Fig. 20 is a schematic illustration of a stimulator control unit 558 positioned external to a patient's body, in accordance with an embodiment of the present invention. At least one flexible electrode 560 preferably extends from control unit 558, through a nostril 562 of the patient, and to a position within the nasal cavity 14 that is adjacent to SPG 6.

It is to be understood that electrodes 557 (Fig. 19) and 560 may each comprise one or more electrodes, e.g., two electrodes, or an array of microelectrodes. For

applications in which stimulator 554 comprises a metal housing that can function as an electrode, then typically one electrode 557 is used, operating in a monopolar mode. Regardless of the total number of electrodes in use, typically only a single or a double electrode extends to SPG 6. Other electrodes 557 or 560 or a metal housing of stimulator 554 are preferably temporarily or permanently implanted in contact with other parts of nasal cavity 2.

Each of electrodes 557 and/or 560 preferably comprises a suitable conductive material, for example, a physiologically-acceptable material such as silver, iridium, platinum, a platinum iridium alloy, titanium, nitinol, or a nickel-chrome alloy. For some applications, one or more of the electrodes have lengths ranging from about 1 to 5 mm, and diameters ranging from about 50 to 100 microns. Each electrode is preferably insulated with a physiologically-acceptable material such as polyethylene, polyurethane, or a co-polymer of either of these. The electrodes are preferably spiral in shape, for better contact, and may have a hook shaped distal end for hooking into or near the SPG. Alternatively or additionally, the electrodes may comprise simple wire electrodes, spring-loaded "crocodile" electrodes, or adhesive probes, as appropriate.

In an embodiment of the invention, each one of electrodes 557 and/or 560 comprises a substantially smooth surface, except that the distal end of each such electrode is configured or treated to have a large surface area. For example, the distal tip may be porous platinized. Alternatively or additionally, at least the tip of electrode 557 or 560, and/or a metal housing of stimulator 554 includes a coating comprising an anti-inflammatory drug, such as beclomethasone sodium phosphate or beclomethasone phosphate. Alternatively, such an anti-inflammatory drug is injected or otherwise applied.

Typically, a determination regarding whether to use a configuration such as that shown in Fig. 19 or that shown in Fig. 20 is made responsive to a frequency or total number of diagnostic procedures anticipated. When this frequency or total number is high, the preference is for a configuration such as that shown in Fig. 19, while one-time or infrequent diagnostic procedures indicates for a configuration such as that shown in Fig. 20.

Fig. 21 is a schematic block diagram illustrating circuitry comprising an implanted unit 20 and an external unit 30, for use with stimulator 554 (Fig. 19), in

accordance with an embodiment of the present invention. Implanted unit 20 preferably comprises a feedback block 22 and one or more sensing or signal application electrodes 24. Implanted unit 20 typically also comprises an electromagnetic coupler 26, which receives power and/or sends or receives data signals to or from an electromagnetic coupler 28 in external unit 30.

External unit 30 preferably comprises a microprocessor 32 which receives an external control signal 34 (e.g., from a physician or from the patient), and a feedback signal 36 from feedback block 22. Control signal 34 may include, for example, operational parameters such as a schedule of operation, patient parameters such as the patient's weight, or signal parameters, such as desired frequencies or amplitudes of a signal to be applied to an MTL. If appropriate, control signal 34 can comprise an emergency override signal, entered by the patient or a healthcare provider to terminate stimulation or to modify it in accordance with a predetermined program. Microprocessor 32, in turn, preferably processes control signal 34 and feedback signal 36 so as to determine one or more parameters of the electric current to be applied through electrodes 24. Responsive to this determination, microprocessor 32 typically generates an electromagnetic control signal 42 that is conveyed by electromagnetic coupler 28 to electromagnetic coupler 26. Control signal 42 preferably corresponds to a desired current or voltage to be applied by electrodes 24 to an MTL, such as SPG 6, and, in an embodiment, inductively drives the electrodes. The configuration of couplers 26 and 28 and/or other circuitry in units 20 or 30 may determine the intensity, frequency, shape, monophasic or biphasic mode, or DC offset of the signal (e.g., a series of pulses) applied to designated tissue.

Power for microprocessor 32 is typically supplied by a battery 44 or, optionally, another DC power supply. Grounding is provided by battery 44 or a separate ground 46. If appropriate, microprocessor 32 generates a display signal 38 that drives a display block 40 of external unit 30. Typically, but not necessarily, the display is activated to show feedback data generated by feedback block 22, or to provide a user interface for the external unit.

Implanted unit 20 is preferably packaged in a case made of titanium, platinum or an epoxy or other suitable biocompatible material. Should the case be made of metal, then the case may serve as a ground electrode and, therefore, stimulation typically is

performed in a monopolar mode. Alternatively, should the case be made of biocompatible plastic material, two electrodes 24 are typically driven to apply current to the MTL.

For some applications, the waveform applied by one or more of electrodes 24 to designated tissue of an MTL (e.g., the SPG) comprises a waveform with an exponential decay, a ramp up or down, a square wave, a sinusoid, a saw tooth, a DC component, or any other shape known in the art to be suitable for application to tissue. Alternatively or additionally, the waveform comprises one or more bursts of short shaped or square pulses -- each pulse may be less than about 1 ms in duration. Generally, appropriate waveforms and parameters thereof are determined during an initial test period of external unit 30 and implanted unit 20. For some applications, the waveform is dynamically updated according to measured physiological parameters, measured during a period in which unit 20 is stimulating an MTL, and/or during a non-activation period.

Fig. 22 is a schematic block diagram of circuitry for use, for example, in conjunction with control unit 558 (Fig. 20), in accordance with an embodiment of the present invention. An external unit 50 comprises a microprocessor 52 supplied by a battery 54 or another DC power source. Grounding may be provided by battery 54 or by a separate ground 56. Microprocessor 52 preferably receives control and feedback signals 58 and 68 (analogous to signal 34 and 36 described hereinabove), and generates responsive thereto a stimulation signal 64 conveyed by one or more electrodes 66 to an MTL or other tissue. Typically, but not necessarily, feedback signal 68 comprises electrical feedback measured by one or more of electrodes 66 and/or feedback from other sensors on or in the patient's brain or elsewhere coupled to the patient's body. If appropriate, microprocessor 52 generates a display signal 60 which drives a display block 62 to output relevant data to the patient or the patient's physician. Typically, some or all of electrodes 66 are temporarily implanted in the patient, and are directly driven by wires connecting the external unit to the implanted unit.

Alternatively or additionally, circuitry may be used that is described in US Provisional Patent Application 60/426,182 to Gross et al., filed November 14, 2002, entitled, "Stimulation circuitry and control of electronic medical device," which is assigned to the assignee of the present patent application and is incorporated herein by reference.

Fig. 23A is a graph schematically illustrating a mode of operation of one or more of the devices shown in Figs. 19-22, in accordance with an embodiment of the present invention. Preferably, the effect of the applied stimulation is monitored by means of a temperature transducer at an MTL (e.g., the SPG) or elsewhere in the head, e.g., in the nasal cavity. As shown in Fig. 23A for a step (ON/OFF) mode of stimulation, stimulation of an MTL or related tissue is initiated at a time T1, and this is reflected by a measurable rise in temperature (due to increased blood flow). Once the temperature rises to a predetermined or dynamically-varying threshold (e.g., 37 °C), stimulation is terminated (time T2), responsive to which the temperature falls. As appropriate, when the temperature drops to a designated or dynamically-determined point, the stimulation is reinitiated (time T3). Preferably, suitable temperatures or other physiological parameters are determined for each patient so as to provide the optimal treatment.

Fig. 23B is a graph schematically illustrating a mode of operation of one or more of the devices shown in Figs. 19-22, in accordance with another embodiment of the present invention. In this embodiment, the amplitude of the waveform applied to an MTL is varied among a continuous set of values (S1), or a discrete set of values (S2), responsive to the measured temperature, in order to achieve the desired performance. It will be appreciated that other feedback parameters measured in the head (e.g., intraocular pressure, intracranial pressure and/or cerebral blood flow), as well as measured systemic parameters (e.g., heart rate) and subjective patient inputs may be used in conjunction with or separately from temperature measurements, in order to achieve generally optimal performance of the implanted apparatus.

Fig. 24 is a graph schematically illustrating a mode of operation of one or more of the devices shown in Figs. 19-22, 32, and 33, in accordance with an embodiment of the present invention. In this embodiment, a drug including a diagnostic agent is administered to the patient at a constant rate, e.g., intravenously, prior to the initiation of chemical, mechanical, electrical and/or odorant stimulation of an MTL at time T1. Advantageously, this prior generation of heightened concentrations of the agent in the blood tends to provide relatively rapid transfer of the agent across the BBB and into the CNS, without unnecessarily prolonging the enhanced permeability of the BBB while waiting for the blood concentration of the agent to reach an appropriate level. Alternatively, for some applications it is desirable to give a single injection of a bolus of

the agent shortly before or after initiation of stimulation of an MTL. Typically, combined administration and stimulation schedules are determined by the patient's physician based on the biochemical properties of each agent targeted at the CNS.

As used in the specification and in the claims, stimulation of an MTL to facilitate transport of a diagnostic agent from the systemic blood circulation to the CNS, is to be understood as including stimulation prior to, during, and/or after administration of the agent to the systemic circulation. For subjects in whom an MTL stimulator previously was implanted for therapeutic purposes, such implanted stimulator may be used for performing stimulation to facilitate a diagnosis, as described herein.

Fig. 25 is a schematic block diagram showing circuitry for parasympathetic stimulation, which is particularly useful in combination with the embodiment shown in Fig. 19, in accordance with an embodiment of the present invention. An external unit 80 preferably comprises a microprocessor 82 that is powered by a battery 84 and/or an AC power source. Microprocessor 82 is grounded through battery 84 or through an optional ground 86.

In a typical mode of operation, an external control signal 88 is input to microprocessor 82, along with a feedback signal 108 from one or more biosensors 106, which are typically disposed in a vicinity of an implanted unit 600 or elsewhere on or in the patient's body. Responsive to signals 88 and 108, microprocessor 82 preferably generates a display signal 89 which drives a display 90, as described hereinabove. In addition, microprocessor 82 preferably processes external control signal 88 and feedback signal 108, to determine parameters of an output signal 592, which is modulated by a modulator 94. The output therefrom preferably drives a current through an electromagnetic coupler 96, which inductively drives an electromagnetic coupler 98 of implanted unit 600. A demodulator 102, coupled to electromagnetic coupler 98, in turn, generates a signal 103 which drives at least one electrode 104 to apply current to an MTL or to other tissue, as appropriate.

Preferably, biosensor 106 comprises implantable or external medical apparatus including, for example, one or more of the following:

- a blood flow sensor,
- a temperature sensor,

- a chemical sensor,
- an ultrasound sensor,
- transcranial Doppler (TCD) apparatus,
- laser-Doppler apparatus,
- 5 • an intraocular pressure sensor, e.g., comprising a piezoelectric crystal or capacitive sensor coupled to the nasal (medial) wall of the orbit, or at another site suitable for measuring intraocular pressure,
- a systemic or intracranial blood pressure sensor (e.g., comprising a piezoelectric crystal or capacitive sensor fixed to a major cerebral blood vessel, capable of detecting a sudden blood pressure increase indicative of a clot),
- 10 • a tissue vitality sensor, e.g., comprising laser Doppler or other optical apparatus for detecting a NAD/NADH ratio in tissue, using optical techniques known in the art for detecting the metabolic state of a tissue,
- 15 • a kinetics sensor, comprising, for example, an acceleration, velocity, or level sensor (e.g., a mercury switch), for indicating body dispositions such as a sudden change in body attitude (as in collapsing),
- an electroencephalographic (EEG) sensor comprising EEG electrodes attached to, or implanted in, the patients head, for indicating changes in neurological patterns, such as symptoms of stroke,
- 20 • a blood vessel clot detector (e.g., as described hereinbelow with reference to Fig. 31), or
- other monitors of physiological quantities suitable for carrying out the objects of this or other embodiments of the present invention.

25 Fig. 26 is a schematic illustration showing operational modes of modulator 94 and/or demodulator 102, in accordance with an embodiment of the present invention. The amplitude and frequency of signal 592 in Fig. 25 can have certain values, as represented in the left graph; however, the amplitude and frequency are modulated so that signal 103 has different characteristics (not necessarily those shown).

Fig. 27 is a schematic illustration of further apparatus for stimulation of an MTL, in accordance with an embodiment of the present invention. In this embodiment, substantially all of the processing and signal generation is performed by circuitry in an implanted unit 110 in the patient, and, preferably, communication with a controller 122 in an external unit 111 is performed only intermittently. The implanted unit 110 preferably comprises a microprocessor 112 coupled to a battery 114. Microprocessor 112 generates a signal 116 that travels along at least one electrode 118 to stimulate the MTL. A feedback signal 120 from a biosensor (not shown) and/or from electrode 118 is received by microprocessor 112, which is adapted to modify stimulation parameters responsive thereto. Preferably, microprocessor 112 and controller 122 are operative to communicate via wireless couplers 126 and 124 (e.g., electromagnetic couplers), in order to exchange data or to change parameters. Further preferably, battery 114 is wirelessly rechargeable (e.g., inductively rechargeable by electromagnetic coupling).

Fig. 28A is a schematic illustration of a stimulator 150, in accordance with an embodiment of the present invention. Preferably, substantially all of the electronic components (including an electronic circuit 158 having a rechargeable energy source) are encapsulated in a biocompatible metal case 154. An inductive coil 156 and at least one electrode 162 are preferably coupled to circuit 158 by means of a feed-through coupling 160. The inductive coil is preferably isolated by an epoxy coating 152, which allows for higher efficiency of the electromagnetic coupling.

Fig. 28B is a schematic illustration of another configuration of an implantable stimulator, in accordance with an embodiment of the present invention. Preferably, substantially all of the electronic components (including an inductive coil 176 and an electronic circuit 178 having a rechargeable energy source) are encapsulated in a biocompatible metal case 174. One or more feed-throughs are preferably provided to enable coupling between at least one electrode 182 and the electronic circuit, as well as between inductive coil 176 and another inductive coil (not shown) in communication therewith.

With reference to Figs. 28A and 28B, the energy source for electronic circuits 158 and 178 may comprise, for example, a primary battery, a rechargeable battery, or a super capacitor. For applications in which a rechargeable battery or a super capacitor is used, any kind of energizing means may be used to charge the energy source, such as

(but not limited to) standard means for inductive charging or a miniature electromechanical energy converter that converts the kinetics of the patient movement into electrical charge. Alternatively, an external light source (e.g., a simple LED, a laser diode, or any other light source) may be directed at a photovoltaic cell in the electronic circuit. Further alternatively, ultrasound energy is directed onto the implanted unit, and transduced to drive battery charging means.

Figs. 29 and 30 are bar graphs showing experimental results obtained during rat experiments performed in accordance with an embodiment of the present invention. A common technique in monitoring bio-distribution of materials in a system includes monitoring the presence and level of radio-labeled tracers. These tracers are unstable isotopes of common elements (e.g., Tc, In, Cr, Ga, and Gd), conjugated to target materials. The chemical properties of the tracer are used as a predictor for the behavior of other materials with similar physiochemical properties, and are selected based on the particular biological mechanisms that are being evaluated. Typically, a patient or experimental animal is placed on a Gamma camera, or target tissue samples can be harvested and placed separately into a well counter. For the purpose of the present set of experiments which were performed, the well counter method was chosen due to its higher sensitivity and spatial resolution. A series of experiments using ⁹⁹Tc-DTPA (DTPA molecule conjugated to a 99-Technetium isotope) were performed. The molecular weight of ⁹⁹Tc-DTPA is 458 Da, its lipophilicity is negative, and its electric charge is +1. These parameters are quite similar to pharmacological agents used in standard chemotherapy, such as tamoxifen, etoposide and irinotecan.

Figs. 29 and 30 show results obtained using ⁹⁹Tc-DTPA penetration assays using ordinary brain sampling techniques (Fig. 29) and peeled brain techniques (Fig. 30). The x-axis of each graph represents different experimental runs, and the y-axis of each graph is defined as: $[(\text{hemisphere radioactivity}) / (\text{hemisphere weight})] / [(\text{total injected radioactivity}) / (\text{total animal weight})]$. The results obtained demonstrate an average 2.5-fold increase in the penetration of ⁹⁹Tc-DTPA to the rat brain. It is noted that these results were obtained by unilateral stimulation of the SPG. The inventors believe that bilateral SPG stimulation will approximately double drug and diagnostic agent penetration, relative to unilateral SPG stimulation.

In both Fig. 29 and Fig. 30, some animals were designated as control animals, and other animals were designated as test animals. In each group, the left and right hemispheres were tested separately, and the height of each bar represents, for a given animal and a given hemisphere, the normalized level of radioactivity as defined above. Thus, Fig. 29 shows results from a total of four test hemispheres and four control hemispheres. Fig. 30 shows results from six test hemispheres and fourteen control hemispheres. The juxtaposition of control and test bars in the bar graphs is not meant to imply pairing of control and test hemispheres.

Fig. 31 is a schematic illustration of acoustic or optical clot detection apparatus 202, for use, for example, in providing feedback to any of the microprocessors or other circuitry described hereinabove, in accordance with an embodiment of the present invention. The detection is preferably performed by coupling to a major blood vessel 200 (e.g., the internal carotid artery or aorta) a detecting element comprising an acoustic or optical transmitter/receiver 206, and an optional reflecting surface 204. Natural physiological liquids may serve as a mediating fluid between the device and the vessel. Preferably, the transmitter/receiver generates an ultrasound signal or electromagnetic signal which is reflected and returned, and a processor evaluates changes in the returned signal to detect indications of a newly-present clot. Alternatively, a transmitter is placed on side of the vessel and a receiver is placed on the other side of the vessel. In either case, for some applications, more than one such apparatus 202 are placed on the vessel, in order to improve the probability of successful clot detection for possible estimation of the clot's direction of motion within the vessel, and to lower the false alarm (i.e. false detection) rate.

Fig. 32 is a schematic illustration of an implantable stimulator 700 for stimulation of an MTL, in accordance with an embodiment of the present invention. Stimulator 700 is preferably implanted adjacent to orbital cavity 708 of a subject. At least one electrode 702 extends from the stimulator to at least one of: an anterior ethmoidal nerve 704 and a posterior ethmoidal nerve 706, which are modulation target locations. Stimulator 700 is preferably implanted through an incision made in the upper edge of the eyelid (not shown).

In an embodiment of the present invention, an odorant is presented to an air passage of a patient, such as a nasal cavity or the throat, so as to increase transport of a

diagnostic agent across the BBB from the systemic blood circulation to the CNS, in order to facilitate a diagnosis of a CNS condition. Alternatively or additionally, an odorant is similarly presented in order to enhance transport of a biochemical agent from the CNS to a non-CNS tissue, such as the systemic blood circulation, in order to
5 facilitate a diagnosis of a CNS condition.

Fig. 33 is a schematic sectional illustration of a nasal inhaler 800, for use in presenting an odorant to a subject, in accordance with an embodiment of the present invention. Nasal inhaler 800 preferably comprises apparatus known in the art, such as an aqueous spray nasal inhaler, a metered dose nasal inhaler, or an air-dilution
10 olfactometer. The odorant is stored in an odorant-storage vessel 802, and is delivered to a nasal passage using an odorant-delivery element 804, such as a nasal piece. Alternatively or additionally, the odorant is presented by means of an orally-dissolvable capsule that releases the active odorants upon contact with salivary liquids. The odorants reach the appropriate neural structures and induce vasodilatation,
15 vasoconstriction and/or cerebrovascular permeability changes.

In an embodiment of the present invention, stimulation of the MTL is achieved by applying a neuroexcitatory agent to the MTL. Suitable neuroexcitatory agents include, but are not limited to acetylcholine and urocholine. For some applications, the MTL is stimulated by applying a neuroinhibitory agent, such as atropine,
20 hexamethonium, or a local anesthetic (e.g., lidocaine).

In an embodiment of the present invention, stimulation of the MTL is achieved by applying mechanical stimulation to the MTL, e.g., vibration.

The stimulation techniques described herein may facilitate the diagnosis of a number of CNS conditions, including, but not limited to, the following conditions:

- 25 • neurodegenerative conditions, such as Alzheimer's disease, Parkinson's Disease, ALS, age-associated cognitive decline, progressive supranuclear palsy, vascular (i.e., multi-infarct) dementia, Lewy body dementia, Huntington's Disease, Down's syndrome, normal pressure hydrocephalus, corticobasal ganglionic degeneration, multisystem
30 atrophy, head trauma, Creutzfeld-Jacob disease, viral encephalitis and hypothyroidism, a degenerative disorder associated with learning, memory or cognitive dysfunction, cerebral senility, multi-infarct

dementia and senile dementia, and electric shock induced amnesia or amnesia;

- neoplastic processes (either primary or metastatic), such as neuroectodermal tumors, malignant astrocytomas, and glioblastomas;
- 5 • immune- and autoimmune-related disorders, such as HIV and multiple sclerosis; and
- CNS inflammatory processes.

The stimulation techniques described herein may facilitate the imaging of various aspects of the CNS, including biochemical aspects (e.g., GGM in late onset Tay-Sachs
10 disease, dopamine in Parkinson's Disease), morphological aspects (e.g., ventricular dimensions in hydrocephalus), and functional aspects (e.g., glucose utilization in brain tumors).

In an embodiment of the present invention, stimulation of an MTL is configured to increase the transport of a diagnostic agent across the BBB from a non-CNS tissue,
15 such as the systemic blood circulation, into the CNS. The diagnostic agent is typically administered to the systemic blood circulation, such as intravenously, and a diagnostic procedure, typically an imaging modality, is then performed directly on the CNS. For some applications, the diagnostic agent comprises a tracer agent, such as an imaging contrast agent, for example, a Magnetic Resonance Imaging (MRI) contrast agent, a
20 Single Photon Emission Computed Tomography (SPECT) radioisotope, a Positron Emission Tomography (PET) radioisotope, an ultrasound contrast enhancer, or an X-ray contrast agent (e.g., for a Computerized Tomography (CT) or angiography imaging sequence).

In an embodiment, the tracer is configured to be disease-specific, typically by
25 conjugation to a biochemical agent for enhancing certain properties or constituents of the CNS (or another physiological compartment). The conjugation is performed either before administration of the agent to the patient, or the conjugation occurs within the systemic circulation, the CNS, or another physiological compartment. Examples of such constituents include selected proteins, cells, biotoxins, pathological tissue, or other
30 biochemical entities that may aid in diagnosis of a CNS condition, such as, for example, the HER2 protein that is overexpressed on the outer membrane of malignant tumors, or

certain interleukins, the receptors of which are abundant on the surface membranes of certain types of cancerous cells. In these applications, the tracer may comprise a disease-specific (endogenous or exogenous) biochemical entity, or may comprise a biochemical entity that relates to a broad group of pathological states (e.g., a probe for inflammatory markers).

For some applications, such diagnostic agents are conjugated to the following types of biochemical agents:

- Antibodies to proteins which are indicative of neoplastic processes, such as beta-Amyloid monoclonal antibody (mAb) or polyclonal antibody (pAb), and anti-HER2 mAb; and/or
- Interleukins (cytokines whose amino acid structure is known), such as IL-1 – IL-18, TNF, IL-1 beta, IL-1ra, and TNF beta. This groups of macromolecules consists of both pro-inflammatory (e.g., IL-6, IL-8) and anti-inflammatory (e.g., IL-4, IL-10) proteins that affect the growth, proliferation, differentiation, regeneration, and secretion of various immuno-active cells (e.g., B, T, CD4+ cells) and also the processes of hematopoiesis and lymphopoiesis. Some of these macromolecules are also produced by immune cells, such as B cells, T cells, macrophages, and acute-phase response proteins. Some of these cytokines are overexpressed by malignant cell lines, as well as in cases of inflammation (e.g., adult T cell leukemia cell lines and Epstein-Barr virus transformed B cells). Such cytokines therefore generally represent diagnostic targets for neoplastic processes.

In an embodiment of the present invention, stimulation of an MTL is configured to increase the transport of a biochemical agent across the BBB from the CNS to a non-CNS tissue, such as the systemic blood circulation. Such biochemical agents are typically disease-specific biochemical markers. Prior to stimulation of an MTL to increase BBB permeability, the concentration of such a biochemical agent is typically greater in the CNS than in the systemic circulation, i.e., there is a concentration gradient across the endothelium. Therefore, increasing the permeability of the BBB, typically acutely, generally releases the agent into the systemic circulation. Once in the systemic circulation, diagnosis is typically performed by sampling a body tissue or fluid, typically

blood, and analyzing the whole blood, plasma, or serum. Analysis is typically performed using a biochemical assay or another analytical procedure, such as imaging, in order to qualitatively or quantitatively probe the presence of the biochemical agent of interest, a metabolite thereof, or a chemical or biological derivative thereof.

5 Diagnostic assay modalities typically applicable to the techniques described herein include, but are not limited to, High Purity Liquid Chromatography (HPLC), SMAC, Enzyme Linked Immuno-Sorbent Assay (ELISA), electrophoresis, gel filtration, UV spectrophotometry, HPLC/fluorescence, Fluorescence Polarization Immunoassay (FPIA), HPLC/UV, Gas Chromatography / GC/EC, capillary electrophoresis, mobility
10 shift combination assay, bioluminescent assay, flow immunoassay, Polymerase Chain Reaction (PCR) ELISA, gamma counter, beta counter, chemiluminescence immunoassay (e.g., chemiluminescent ELISA), Dissociated Enhanced Lanthanide Fluorescence Immunoassay (DELFIA), Enzyme Immunoassay (EIA), Fluorescence Immunoassay (FIA), Immunoradiometric Assay (IRMA), Radioimmunoassay (RIA),
15 and Scintillation Proximity Assay (SPA).

Imaging modalities typically applicable to the techniques described herein include, but are not limited to, PET, SPECT, CT, MRI, magnetic resonance spectroscopy (MRS), Functional Magnetic Resonance Imaging (fMRI), Proton MRSI, Single-voxel proton MRS, Multi-nuclear MRS, gamma camera, and beta camera.

20 For some applications, techniques for transporting diagnostic agents from the systemic circulation to the CNS are used to transport one or more of the following radioisotopes for facilitating nuclear imaging modalities, such as PET, SPECT, and gamma cameras: ^7Be , ^{22}Na , ^{46}Sc , ^{48}V , ^{51}Cr , ^{54}Mn , ^{56}Co , ^{65}Zn , ^{75}Se , ^{83}Rb , ^{85}Sr , ^{88}Zr , $^{95\text{m}}\text{Tc}$, ^{103}Ru , and ^{99}Rh . These techniques may also be used for transporting
25 one or more of the following diagnostic agents for facilitating PET: ^{18}F -FDG, ^{18}F -FUDR, ^{11}C -MET, ^{11}C -TYR, ^{15}C -O₂, ^{15}C -O, H₂¹⁵O, ^{82}Rb , ^{11}C -5-HTP, ^{11}C -L-DOPA, ^{11}C -L-DEP, U-5-HIAA, $^{99\text{m}}\text{Tc}$, ^{201}Tl , ^{111}In -Oncoscint, and ^{150}O . These techniques may also be used for transporting one or more of the following diagnostic agents for facilitating SPECT: I-123 ligands (e.g., I-123-IMP, Iodine-123-QNB, Iodine-
30 123-Iodine labeled ligands IBZM and IBZP), Tc-99m ligands (e.g., Tc-99m-hexamethyl propylamine oxime, Tc-Technetium-99m-bicisate), and Xenon-133 ligands.

The techniques described herein may also be used to transport the diagnostic agents and types of diagnostic agents shown in the following table. Although the agents are categorized by typical diagnostic aims for which they are generally appropriate, the techniques described herein are not limited to facilitating transport for these diagnostic

5 aims.

Cell proliferation	^{11}C -TdR, ^{18}F -3'FLT, ^{124}I -IUdR, ^{76}Br -FbrAU
<u>Angiogenesis</u>	
Blood flow	^{15}O -water, $^{99\text{m}}\text{Tc}$ -sestamibi, ^{201}Tl -thallium, ^{133}Xe -saline
Blood volume	^{15}O - or ^{11}C -carbon monoxide-labeled erythrocytes (RBCs), $^{99\text{m}}\text{Tc}$ -RBCs
Capillary permeability	^{82}Rb , ^{68}Ga -DTPA, ^{68}Ga -transferrin, ^{18}F -, ^{123}I -, ^{131}I -, ^{124}I - or $^{99\text{m}}\text{Tc}$ - labeled albumin
Oxygen metabolism	^{15}O (oxygen)
Hypoxia	^{18}F -fluoromisonidazole, ^{61}Cu - or ^{64}Cu -ATSM, ^{18}F -EF1, ^{18}F -EF5
<u>Transporter up-regulation</u>	
Amino acid transporters	^{11}C -methionine, ^{18}F -FET, ^{18}F -FACBC
	^{11}C -FMAU
Nucleoside transporters	^{18}F -fluorocholine
Choline transporter	^{11}C -3OMG, ^{18}F -FDG
Glucose transporter	
<u>Cell surface receptors/antigens (endothelial</u>	

<u>cells and tumor cells)</u> Transferrin receptors EGF receptor (radiolabeled antibody or peptide) Benzodiazepine receptor Other cell surface receptors/antigens (e.g., Flt1 and Flk1/KDR receptors for VEGF)	 ^{67}Ga -transferrin, ^{111}In -DTPA transferrin chelate iodinated-PK11195
Cell matrix antigens	Integrins (RGD- and other radiolabeled peptides)

For some applications, techniques for transporting diagnostic agents from the systemic circulation to the CNS are used to transport one or more of the following contrast agents for facilitating MRI: gadolinium chelates (e.g., Gd-DTPA, Gd-DOTAP, Gd-EOB-DTPA), manganese chelates, paramagnetic iron oxide particles (e.g., polydisperse iron oxide particles, with a partial dextran coat, or ultrasmall superparamagnetic iron oxide - USPIO), and hyperpolarized gases (e.g., ^3He / ^{129}Xe).

For some applications, techniques for transporting diagnostic agents from the systemic circulation to the CNS are used to transport one or more of the following contrast agents for facilitating ultrasound imaging: polymer microbubbles, microscopic bubbles (e.g., *Imavist*TM), investigational agent PB127-filled (polylactide/albumin) or nitrogen-filled microspheres, and iron oxide particles called ferumoxtran.

For some applications, techniques for transporting diagnostic agents from the systemic circulation to the CNS are used to transport one or more of the following contrast agents for facilitating CT: radiopaque tracers (e.g., dysprosium-, iodine- and gadolinium-based contrast agents) and stable xenon gas.

For some applications, techniques for transporting diagnostic agents from the systemic circulation to the CNS are used to transport diagnostic agents for facilitating optical intrinsic signal (OIS) imaging.

For some applications, the stimulation techniques described herein are used to facilitate diagnosis of Alzheimer's disease or other conditions of the CNS in conjunction with techniques described in the following patents. It should be appreciated by those of skill in the art that the following techniques are set forth for demonstrative purposes.

- 5 However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

US Patent 4,666,829 to Glenner et al., which is incorporated herein by reference, describes a polypeptide and fragments thereof that may be used to produce antibodies
10 useful in a diagnostic test for Alzheimer's disease. Nucleotide probes corresponding to portions of the polypeptide are also described as useful for diagnostic purposes. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of diagnostic agents from the systemic blood circulation to the CNS are used in conjunction with techniques described in the '829 patent.

- 15 US Patent 4,874,694 to Gandy et al., which is incorporated herein by reference, describes a diagnostic method for neurological and psychiatric disorders, utilizing the cerebrospinal fluid incubated in the presence of 32-P labeled ATP and an appropriate protein kinase. After termination of the reaction, a sample is applied to gels for electrophoresis. Subsequent autoradiography results in a disease-specific protein pattern
20 that can be used for diagnosis of disorders such as Alzheimer disease, Huntington disease, Parkinson disease, dystonia ataxia, schizophrenia, epilepsy brain tumors, brain irradiation, head trauma, and acute and chronic encephalitic and vascular disease. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood
25 circulation are used in conjunction with techniques described in the '694 patent.

US Patent 6,358,681 to Ginsberg et al., which is incorporated herein by reference, describes methods for detecting RNA in brain tissue in order to diagnose Alzheimer's disease. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the
30 systemic blood circulation are used in conjunction with techniques described in the '681 patent.

US Patent 6,329,531 to Turner et al., which is incorporated herein by reference, describes the use of optical diagnostic agents in in vivo and in vitro diagnosis of neurodegenerative diseases such as Alzheimer's disease by means of near infra-red radiation (NIR radiation) as a contrasting agent in fluorescence and transillumination diagnosis in the NIR range. Diagnostic agents containing such components are also described. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of diagnostic agents from the systemic blood circulation to the CNS are used in conjunction with techniques described in the '531 patent.

US Patent 6,287,793 to Schenk et al., which is incorporated herein by reference, describes methods for identifying key diagnostic antibodies and antigens characteristic of a disease state of interest, such as Alzheimer's disease.

US Patent 6,210,895 to Schipper et al., which is incorporated herein by reference, describes a method for predicting the onset of, diagnosing, and/or prognosticating dementing diseases. The method comprises determining the concentration of heme oxygenase-1 (HO-1) and/or a nucleotide sequence encoding HO-1 in tissue obtained from a patient, and comparing said concentration with the corresponding concentration of HO-1 and/or an HO-1 encoding nucleotide sequence in corresponding tissue obtained from at least one control person. The tissue is typically plasma, lymphocytes, cerebrospinal fluid or fibroblasts. The method is described as being useful where the dementing disease is any of Alzheimer's disease, Age-Associated Cognitive Decline, Progressive Supranuclear Palsy, Vascular (i.e., multi-infarct) Dementia, Lewy Body Dementia, Huntington's Disease, Down's syndrome, normal pressure hydrocephalus, corticobasal ganglionic degeneration, multisystem atrophy, head trauma, Creutzfeldt-Jacob disease, viral encephalitis and hypothyroidism. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with techniques described in the '895 patent.

US Patent 6,200,768 to Mandelkow et al., which is incorporated herein by reference, describes (a) epitopes of the protein which are specifically occurring in a phosphorylated state in tau protein from Alzheimer paired helical filaments, (b) protein kinases which are responsible for the phosphorylation of the amino acids of the tau protein giving rise to said epitopes, and (c) antibodies specific for said epitopes. The

patent also describes pharmaceutical compositions for the treatment or prevention of Alzheimer's disease, diagnostic compositions and methods for the detection of Alzheimer's disease, and the use of said epitopes for the generation of antibodies specifically detecting Alzheimer tau protein. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with techniques described in the '768 patent. For some applications, these techniques facilitate increased release of said epitopes of the phosphorylated tau into the systemic circulation, after which a body fluid is analyzed for the presence of the epitopes or chemical/biological derivatives thereof.

US Patent 6,132,977 to Thompson et al., which is incorporated herein by reference, describes methods for the immunological identification and quantitation of SNAP-25 in a biological fluid, especially cerebrospinal fluid and amniotic fluid. The quantitated levels of SNAP-25 serve as a diagnostic marker for some mental illnesses such as major depression, Alzheimer's disease and schizophrenia. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with techniques described in the '977 patent, in order to release the SNAP-25 into the systemic circulation and thereafter analyze body fluid for epitopes and/or chemical/biological derivatives thereof.

US Patent 6,114,175 to Klunk et al., which is incorporated herein by reference, describes methods using amyloid binding compounds which are non-azo derivatives of Chrysamine G, to identify Alzheimer's brain in vivo and to diagnose other pathological conditions characterized by amyloidosis, such as Down's Syndrome. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with techniques described in the '175 patent.

Other patents describe methods for aiding in the diagnosis of Alzheimer's disease by measuring amyloid-beta peptide levels in a CSF sample of the patient. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of diagnostic agents from the systemic blood circulation to the CNS are used in conjunction with these methods, in order to increase the permeability of the

BBB to transport labeled (e.g., radiolabeled) amyloid-beta mAb or pAb into the CNS and thereafter perform imaging to assess the amount of amyloid-beta peptide. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with these methods. After transport across the BBB has been facilitated, high levels of amyloid-beta peptide in body fluid are considered inconsistent with a diagnosis of Alzheimer's disease, while low levels may indicate a rationale for further inquiries, and may also indicate an increased probability of Alzheimer's disease.

US Patent 6,130,048 to Nixon, which is incorporated herein by reference, describes a method for diagnosing Alzheimer's disease by measuring the level of a lysosomal hydrolase or lysosomal protease inhibitor in a patient's cerebrospinal fluid. Also described are methods for measuring the progression of the disease and for screening therapeutic compositions for treating the disease. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with techniques described in the '048 patent.

US Patent 6,087,118 to Aronson et al., which is incorporated herein by reference, describes a method for diagnosing Alzheimer's disease using human blood platelets, wherein the presence or absence of functioning calcium-dependent potassium channels in blood platelets are determined by employing potassium channel blockers such as apamin or charybdotoxin, the absence of functioning calcium-dependent potassium channels indicating a positive diagnosis for Alzheimer's disease. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with techniques described in the '118 patent. It is hypothesized by the inventor of the present invention that increasing the permeability of the BBB increases the interaction between the intra-cephalic environment and the systemic circulation, thereby increasing the efficacy and statistical accuracy of the method described in the '118 patent.

US Patent 6,071,705 to Wands et al., which is incorporated herein by reference, describes a method for detecting and diagnosing neurological disease or dysfunction,

such as Alzheimer's disease and Down's Syndrome, using antibodies against a neurological form of Pancreatic Thread Protein (nPTP), such antibodies including monoclonal antibodies, a combination of those monoclonal antibodies, or nucleic acid probes. In an embodiment of the present invention, stimulation techniques described
5 herein for facilitating transport of diagnostic agents from the systemic blood circulation to the CNS are used in conjunction with techniques described in the '705 patent, in order to increase the permeability of the BBB to transport labeled (e.g., radiolabeled) antibodies of nPTP into the CNS and thereafter perform imaging to assess the amount of nPTP bound to the labeled antibodies. Alternatively or additionally, stimulation
10 techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with techniques described in the '705 patent, in order to increase the release of nPTP into the systemic circulation and thereafter sample a body fluid and analyze it for the presence of nPTP.

US Patent 6,001,331 to Caprathe et al., which is incorporated herein by
15 reference, describes a method of imaging amyloid deposits, and radiolabeled compounds useful in imaging amyloid deposits. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of diagnostic agents from the systemic blood circulation to the CNS are used in conjunction with techniques described in the '331 patent, in order to increase the delivery of the radiolabeled
20 compounds into the CNS, thereby enhancing the contrast of the plaque.

US Patent 5,985,581 to Nixon et al., which is incorporated herein by reference, describes a method of diagnosing Alzheimer's disease utilizing presenilin-1, whose level is found to be substantially decreased in Alzheimer's patients. A CSF sample (ventricular or lumbar) is taken, and the level of presenilin-1 is measured using an
25 immunoassay that uses antibodies to presenilin-1, to a fragment thereof, or to a specific amino acid sequence. In an embodiment of the present invention, the antibodies, antibody fragments, or specific amino acid sequence described in the '581 patent are labeled (e.g., radiolabeled) to facilitate a subsequent imaging procedure for assessing the amount of bound presenilin-1. The stimulation techniques described herein for
30 facilitating transport of diagnostic agents from the systemic blood circulation to the CNS are used to deliver the labeled compounds to the CNS. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in

conjunction with techniques described in the '581 patent, in order to increase the penetration of the abovementioned proteins from the CNS into the systemic circulation and thereafter analyze a body fluid using the methods and/or diagnostic kits described in the '581 patent. Levels of the protein that are higher than a threshold value may indicate
5 the absence of Alzheimer's disease.

US Patent 5,981,194 to Jefferies et al., which is incorporated herein by reference, describes methods for using p97 and iron-binding proteins as diagnostic and therapeutic agents, including for the diagnosis of Alzheimer's disease. The methods are based on evidence that Alzheimer's patients have elevated levels of elevated levels of p97 in their
10 serum and cerebrospinal fluid and that p97 levels increase with duration of the disease. The levels of p97 in patient samples may thus be used to diagnose and to monitor the progression of the disease and the efficacy of therapeutic treatments for Alzheimer's disease. Evidence is also presented that microglial cells associated with senile plaques in Alzheimer's disease express p97 and transferrin receptor. Therefore, p97 and
15 transferrin receptor can be used in the diagnosis of Alzheimer's Disease. The finding that microglial cells which deposit the amyloid protein have a high level of proteins which operate in procurement of iron also suggests methods of treatment of Alzheimer's disease based on depletion of iron from these cells using substances such as p97, transferrin, and iron chelators, for example, lactoferrin, ferritin, and ovotransferrin. In
20 an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with techniques described in the '194 patent. The use of these techniques in combination typically enhances the accuracy of diagnosis of Alzheimer's disease.

US Patent 5,849,600 to Nixon et al., which is incorporated herein by reference, describes a method for diagnosing Alzheimer's disease in a human patient by measuring the amount of p33 present in a biological sample, such as a ventricular or lumbar CSF sample, or brain tissue homogenate. In an embodiment of the present invention, the stimulation techniques described herein are used to facilitate transport of a labeled (e.g.,
25 radiolabeled) anti-p33 mAb or pAb from the systemic circulation to the CNS. An imaging procedure is subsequently performed to evaluate the amount of p33 protein in the CNS. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic
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blood circulation are used in conjunction with techniques described in the '600 patent, in order to increase the penetration of the abovementioned protein from the CNS into the systemic circulation. Thereafter a body fluid is analyzed using the methods and/or diagnostic kits described in the '600 patent. Levels of the protein that are higher than a threshold value may indicate the presence of Alzheimer's disease.

US Patent 5,833,988 to Friden, which is incorporated herein by reference, describes a method for delivering a neuropharmaceutical or diagnostic agent across the BBB to the brain. The method comprises administering to the host a therapeutically effective amount of an antibody-neuropharmaceutical or diagnostic agent conjugate wherein the antibody is reactive with a transferrin receptor. In an embodiment of the present invention, the stimulation techniques described herein are used to facilitate transport of an agent described in the '988 patent from the systemic circulation to the CNS. An imaging procedure is subsequently performed to evaluate the amount of a ligand of the agent in the CNS.

US Patent 5,830,670 to de la Monte et al., which is incorporated herein by reference, describes a method for diagnosing Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, and glioblastomas, by identifying recombinant hosts and vectors which contain the genes coding for neuronal thread proteins (NTPs) associated with these conditions. Specific targeted NTPs have molecular weights of about 8 kDa, about 14 kDa, about 17 kDa, about 21 kDa, about 26 kDa or about 42 kDa. In an embodiment of the present invention, the stimulation techniques described herein are used to facilitate transport of a labeled (e.g., radiolabeled) antibody against an NTP from the systemic circulation to the CNS. An imaging procedure is subsequently performed to evaluate the amount of the NTP in the CNS. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of biochemical agents from the CNS to the systemic blood circulation are used in conjunction with techniques described in the '670 patent, in order to increase the penetration of the abovementioned protein from the CNS into the systemic circulation. Thereafter in vivo or in vitro analysis of body fluid is performed, typically using a diagnostic kit. Levels of the protein that are higher than a threshold value may indicate the presence of Alzheimer's disease or other conditions described in the '670 patent.

In an embodiment of the present invention, stimulation techniques described herein are used to facilitate a diagnosis of brain tumors (primary and secondary (metastatic) neoplasms in the brain). Such stimulation typically facilitates the transfer from the systemic circulation to the CNS of a labeled (e.g., radiolabeled) diagnostic agent, which may be specific for the neoplasm to be diagnosed, for a group of neoplasms, or generally for a pathologic state in the CNS.

For example, these stimulation techniques may be used to diagnosis gliomas. Gliomas often overexpress a receptor for interleukin 13 (IL-13). Because interleukins have large molecular sizes (typically, ten of kilodaltons), they generally penetrate the CNS poorly under a wide range of physiological conditions. In conjunction with administration of labeled IL-13 into the systemic circulation, an MTL is stimulated, allowing the IL-13 to pass into the CNS, where the IL-13 typically concentrates in tumor locations. Such concentration is detected using an imaging procedure. This approach typically represents a relatively low-risk and highly disease-specific approach to diagnosing such tumors.

Another example is the use of labeled (e.g., radiolabeled) anti-HER2 mAb or pAb for imaging of breast cancer metastases in the brain. HER2 is a protein over-expressed on the malignant cell outer membrane in a significant percentage of patients with breast cancer. The permeability of the BBB is increased using the stimulation techniques described herein, in conjunction with administration of labeled anti-HER2 mAb or pAb and performance of an imaging procedure. This approach typically represents a relatively low-risk and highly disease-specific approach to diagnosing such metastases.

In an embodiment, methods are used for aiding the diagnosis of brain tumors or screening for brain tumors. Typically, these methods include using labeled interleukins, anti-cancer-cells mAb/pAb or other possible markers of neoplasms in conjunction with an imaging procedures. In an embodiment of the present invention, stimulation techniques described herein for facilitating transport of diagnostic agents from the systemic blood circulation to the CNS are used to transport labeled (e.g., radiolabeled) amyloid-beta mAb or pAb into the CNS, and a subsequent imaging procedure is performed.

In an embodiment of the present invention, the stimulation techniques described herein are used to facilitate increased release of disease-related agents (e.g., proteins, DNA fragments, etc.) from the CNS into the systemic circulation and body tissues. To diagnose brain tumors, these techniques are used to facilitate the transport of markers of the central malignant process (e.g. glioma) from the CNS to the systemic circulation, where they are detected using a suitable bioassay.

For some applications, the diagnostic techniques described herein are used at more than one point in time in order to indicate the possible progression of the CNS condition being diagnosed.

Some existing and proposed diagnostic techniques use a sample of CSF for biochemical analysis. In an embodiment of the present invention, stimulation techniques described herein are used to increase transport of biochemical markers from the CSF to the systemic circulation as an alternative to direct sampling of the CSF.

"Diagnosis," as used in the present patent application, including the claims, is to be understood as comprising the art or act of recognizing the presence of disease from its signs or symptoms, deciding as to the character (e.g., stage) of a disease, screening for disease, and/or predicting the onset of disease. Diagnosis may be performed in vivo or in vitro, as appropriate. Diagnosis may comprise a combination of diagnostic procedures. For example, the permeability of the BBB may be increased in combination with taking a blood sample and analyzing it for the presence of a biochemical marker of a CNS neoplastic process, and performing PET imaging for a mAb or pAb to a protein that is indicative of a neoplastic process.

In some embodiments of the present invention, techniques described herein are practiced in combination with techniques described in one or more of the references cited in the Background section hereinabove and/or in combination with techniques described in one or more of the patent applications cited hereinabove.

Techniques described in this application may be practiced in combination with methods and apparatus described in one or more of the following patent applications, which are assigned to the assignee of the present patent application and are incorporated herein by reference:

- US Patent Application 10/258,714, filed October 25, 2002, entitled, "Method and apparatus for stimulating the sphenopalatine ganglion to modify properties of the BBB and cerebral blood flow," or the above-referenced PCT Publication WO 01/85094
- 5 • US Provisional Patent Application 60/364,451, filed March 15, 2002, entitled, "Applications of stimulating the sphenopalatine ganglion (SPG)"
- US Provisional Patent Application 60/368,657, filed March 28, 2002, entitled, "SPG Stimulation"
- 10 • US Provisional Patent Application 60/376,048, filed April 25, 2002, entitled, "Methods and apparatus for modifying properties of the BBB and cerebral circulation by using the neuroexcitatory and/or neuroinhibitory effects of odorants on nerves in the head"
- US Provisional Patent Application 60/388,931, filed June 14, 2002, entitled "Methods and systems for management of Alzheimer's disease"
- 15 • US Provisional Patent Application 60/400,167, filed July 31, 2002, entitled, "Delivering compounds to the brain by modifying properties of the BBB and cerebral circulation"
- US Provisional Patent Application 60/426,180, filed November 14, 2002, entitled, "Surgical tools and techniques for sphenopalatine ganglion stimulation"
- 20 • US Provisional Patent Application 60/426,182, filed November 14, 2002, and a corresponding PCT application claiming priority therefrom, filed November 13, 2003, entitled, "Stimulation circuitry and control of electronic medical device"
- US Patent Application 10/294,310, filed November 14, 2002, entitled, "SPG stimulation for treating eye pathologies"
- 25 • US Patent Application US 10/294,343, filed November 14, 2002, and a corresponding PCT application claiming priority therefrom, filed November 13, 2003, entitled, "Administration of anti-inflammatory drugs into the CNS"
- US Provisional Patent Application 60/426,181, filed November 14, 2002, entitled, "Stimulation for treating ear pathologies"

- US Provisional Patent Application 60/448,807, filed February 20, 2003, entitled, "Stimulation for treating autoimmune-related disorders of the CNS"
- US Provisional Patent Application 60/461,232 to Gross et al., filed April 8, 2003, entitled, "Treating abnormal conditions of the mind and body by modifying properties of the blood-brain barrier and cephalic blood flow"
- a PCT Patent Application to Shalev, filed April 25, 2003, entitled, "Methods and apparatus for modifying properties of the BBB and cerebral circulation by using the neuroexcitatory and/or neuroinhibitory effects of odorants on nerves in the head"
- a US provisional patent application, filed September 26, 2003, entitled, "Diagnostic applications of stimulation"
- a US patent application, filed October 2, 2003, entitled, "Targeted release of nitric oxide in the brain circulation for opening the BBB"
- a PCT patent application, filed November 13, 2003, entitled, "Stimulation for treating ear pathologies"
- a PCT patent application, filed November 13, 2003, entitled, "Surgical tools and techniques for stimulation"

As used in the present application and in the claims, the BBB comprises the tight junctions opposing the passage of most ions and large molecular weight compounds between the blood and brain tissue.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and subcombinations of the various features described hereinabove, as well as variations and modifications thereof that are not in the prior art, which would occur to persons skilled in the art upon reading the foregoing description. For example, elements which are shown in a figure to be housed within one integral unit may, for some applications, be disposed in a plurality of distinct units. Similarly, apparatus for communication and power transmission which are shown to be coupled in a wireless fashion may be, alternatively, be coupled in a wired fashion, and apparatus for communication and power transmission which are

shown to be coupled in a wired fashion may be, alternatively, be coupled in a wireless fashion.

CLAIMS

1. Apparatus for treating a subject, comprising:
an elongated generally rigid support element having a length of at least 1.8 cm,
and having a distal end;
5 one or more electrodes fixed to the support element in a vicinity of the distal end thereof, and configured to be positioned in a vicinity of a site of the subject when the support element is inserted into a body of the subject, such that a portion of the support element remains outside of the body, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a
10 lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject,
15 and a lesser deep petrosal nerve of the subject; and
a control unit, coupled to the support element, and adapted to drive the electrodes to apply an electrical current to the site, and to configure the current to increase cerebral blood flow (CBF) of the subject, so as to treat a condition of the subject.
2. The apparatus according to claim 1, wherein the condition includes an acute
20 ischemic condition of a brain of the subject, and wherein the control unit is adapted to configure the current to increase the CBF to a level sufficient to treat the acute ischemic condition of the brain.
3. The apparatus according to claim 1, wherein the condition includes a
25 complication of subarachnoid hemorrhage (SAH) of the subject, and wherein the control unit is adapted to configure the current to increase the CBF to a level sufficient to treat the complication.
4. The apparatus according to claim 1, wherein the condition includes an acute brain injury of the subject, and wherein the control unit is adapted to configure the current to increase the CBF to a level sufficient to treat the acute brain injury.

5. The apparatus according to claim 1, wherein the condition includes vasospasm after stroke of the subject, and wherein the control unit is adapted to configure the current to increase the CBF to a level sufficient to treat the vasospasm after stroke.
6. The apparatus according to claim 1, wherein the condition includes traumatic brain injury (TBI) of the subject, and wherein the control unit is adapted to configure the current to increase the CBF to a level sufficient to treat the TBI.
7. The apparatus according to claim 1, wherein the condition includes a seizure of the subject, and wherein the control unit is adapted to configure the current to increase the CBF to a level sufficient to treat the seizure.
8. The apparatus according to claim 1, wherein the site includes the SPG of the subject, and wherein the electrodes are configured to be positioned in the vicinity of the SPG.
9. The apparatus according to claim 1, wherein the support element is substantially straight.
10. The apparatus according to claim 1, wherein the support element has a length between about 7 cm and about 13 cm.
11. The apparatus according to claim 1, wherein a portion of the support element adapted for insertion into the body has a length of between about 2.5 cm and about 3 cm.
12. The apparatus according to claim 1, wherein the control unit is adapted to configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.
13. The apparatus according to any one of claims 1-12, wherein the condition includes occlusion within a retinal circulation of the subject, and wherein the control unit is adapted to configure the current to increase retinal blood flow of the subject to a level sufficient to treat the occlusion within the retinal circulation.
14. The apparatus according to claim 13, wherein the occlusion includes retinal artery occlusion (RAO) of the subject, and wherein the control unit is adapted to

configure the current to increase the retinal blood flow to a level sufficient to treat the RAO.

15. The apparatus according to claim 13, wherein the occlusion includes retinal venous occlusion (RVO) of the subject, and wherein the control unit is adapted to
5 configure the current to increase the retinal blood flow to a level sufficient to treat the RVO.

16. The apparatus according to any one of claims 1-12, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a roof of an oral cavity of the subject.

10 17. The apparatus according to claim 16, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a greater palatine canal of the subject.

18. The apparatus according to any one of claims 1-12, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a nose of the
15 subject.

19. The apparatus according to claim 18, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a sphenopalatine foramen of the subject.

20. The apparatus according to any one of claims 1-12, wherein the support element
20 comprises at least one mark, adapted to indicate a depth of insertion of the support element in the body.

21. The apparatus according to claim 20, wherein a distance of the mark from the distal end of the support element is between about 2.5 cm and about 3 cm.

22. The apparatus according to any one of claims 1-12, wherein the support element
25 comprises a stopper, adapted to prevent insertion of the support element into the body beyond a certain depth.

23. The apparatus according to claim 22, wherein a distance of the stopper from the distal end of the support element is between about 2.5 cm and about 3 cm.

24. The apparatus according to any one of claims 1-12, wherein the support element
30 is bent at one or more locations.

25. The apparatus according to claim 24, wherein an angle of a bend of the support element is between about 20 and about 40 degrees.
26. The apparatus according to claim 24, wherein a distance of a bend of the support element from the distal end of the support element is between about 2 cm and about 3
5 cm.
27. Apparatus for treating a complication of subarachnoid hemorrhage (SAH) of a subject, comprising:
a medical vehicle, adapted to directly treat the SAH; and
a stimulator adapted to stimulate at least one site of the subject, so as to treat a
10 complication arising from use of the medical vehicle, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an
15 efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject.
28. The apparatus according to claim 27, wherein the site includes the SPG of the subject, and wherein the stimulator is adapted to stimulate the SPG.
- 20 29. The apparatus according to claim 27, wherein the stimulator is adapted to configure the stimulation to increase cerebral blood flow (CBF) of the subject.
30. The apparatus according to claim 27, wherein the medical vehicle comprises a tool for clipping an aneurysm that caused the SAH.
31. The apparatus according to claim 27, wherein the medical vehicle comprises a
25 pharmaceutical composition for treating an aneurysm that caused the SAH.
32. The apparatus according to claim 27, wherein the stimulator comprises an electrical stimulator, adapted to apply an electrical current to the site.
33. The apparatus according to claim 27, wherein the stimulator comprises a magnetic stimulator, adapted to apply a magnetic field to the site.

34. The apparatus according to claim 27, wherein the stimulator comprises a chemical stimulator, adapted to apply a chemical to the site.

35. The apparatus according to claim 27, wherein the stimulator comprises a mechanical stimulator, adapted to apply mechanical energy to the site.

5 36. Apparatus for treating a condition of a subject, comprising:

a coil, adapted to be positioned in a vicinity of a site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

10 a control unit, adapted to drive the coil to generate a magnetic field in the vicinity of the site capable of inducing an increase in cerebral blood flow (CBF) of the subject.

37. The apparatus according to claim 36, wherein the site includes the SPG of the subject, and wherein the coil is adapted to be positioned in the vicinity of the SPG.

38. The apparatus according to claim 36, wherein the control unit is adapted to generate the magnetic field with a strength sufficient to stimulate the site, and
20 insufficient to substantially stimulate brain tissue of the subject.

39. The apparatus according to claim 36, comprising a cooling element, adapted to prevent excessive heating of the coil.

40. The apparatus according to claim 36, wherein the coil comprises between about 4 and about 30 loops of wire.

25 41. The apparatus according to any one of claims 36-40, wherein the coil is adapted to be inserted into a nasal cavity of the subject.

42. The apparatus according to claim 41, wherein the coil is substantially figure-eight-shaped.

43. The apparatus according to claim 41, wherein the coil is substantially 4-leaf-
30 shaped.

44. The apparatus according to claim 41, wherein the coil is substantially circular.
45. The apparatus according to claim 41, wherein the coil has a diameter of between about 3 mm and about 12 mm.
46. The apparatus according to any one of claims 36-40, wherein the coil is adapted
5 to be placed in a vicinity of a temporomandibular joint of the subject.
47. The apparatus according to claim 46, wherein the coil has a diameter of between about 3 cm and about 12 cm.
48. The apparatus according to any one of claims 36-40, wherein the coil is adapted to be placed around at least a portion of a head of the subject.
- 10 49. The apparatus according to claim 48, wherein the coil has a diameter of between about 3 cm and about 12 cm.
50. Apparatus for treating a condition of a subject, comprising:
a coil, adapted to be positioned in a vicinity of a site selected from the list
consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of
15 the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a
communicating branch between a maxillary nerve and an SPG of the subject, an otic
ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an
efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the
subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject,
20 and a lesser deep petrosal nerve of the subject; and
a control unit, adapted to drive the coil to generate a magnetic field in the vicinity
of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB)
of the subject.
51. The apparatus according to claim 50, wherein the site includes the SPG of the
25 subject, and wherein the coil is adapted to be positioned in the vicinity of the SPG.
52. The apparatus according to claim 50, wherein the control unit is adapted to
generate the magnetic field with a strength sufficient to stimulate the site, and
insufficient to substantially stimulate brain tissue of the subject.
53. The apparatus according to claim 50, comprising a cooling element, adapted to
30 prevent excessive heating of the coil.

54. The apparatus according to claim 50, wherein the coil comprises between about 4 and about 30 loops of wire.
55. The apparatus according to any one of claims 50-54, wherein the coil is adapted to be inserted into a nasal cavity of the subject.
- 5 56. The apparatus according to claim 55, wherein the coil is substantially figure-eight-shaped.
57. The apparatus according to claim 55, wherein the coil is substantially 4-leaf-shaped.
58. The apparatus according to claim 55, wherein the coil is substantially circular.
- 10 59. The apparatus according to claim 55, wherein the coil has a diameter of between about 3 mm and about 12 mm.
60. The apparatus according to any one of claims 50-54, wherein the coil is adapted to be placed in a vicinity of a temporomandibular joint of the subject.
61. The apparatus according to claim 60, wherein the coil has a diameter of between
15 about 30 mm and about 120 mm.
62. The apparatus according to any one of claims 50-54, wherein the coil is adapted to be placed around at least a portion of a head of the subject.
63. The apparatus according to claim 62, wherein the coil has a diameter of between about 10 cm and about 25 cm.
- 20 64. Apparatus for facilitating a diagnosis of a condition of a subject, comprising:
an elongated generally rigid support element having a length of at least 1.8 cm,
and having a distal end;
one or more electrodes fixed to the support element in a vicinity of the distal end
thereof, and configured to be positioned in a vicinity of a site of the subject when the
25 support element is inserted into a body of the subject, such that a portion of the support
element remains outside of the body, the site selected from the list consisting of: a
sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a
lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a
communicating branch between a maxillary nerve and an SPG of the subject, an otic
30 ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an

efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

a control unit, coupled to the support element, and adapted to:

- 5 drive the electrodes to apply an electrical current to the site, and
 configure the current to induce an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a diagnostic agent across the BBB into a central nervous system (CNS) of the subject.

65. The apparatus according to claim 64, wherein the site includes the SPG of the
10 subject, and wherein the electrodes are configured to be positioned in the vicinity of the SPG.

66. The apparatus according to claim 64, wherein the support element is substantially straight.

67. The apparatus according to claim 64, wherein the support element has a length
15 between about 7 cm and about 13 cm.

68. The apparatus according to claim 64, wherein a portion of the support element adapted for insertion into the body has a length of between about 2.5 cm and about 3 cm.

69. The apparatus according to claim 64, wherein the control unit is adapted to
20 configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

70. The apparatus according to any one of claims 64-69, wherein the support element
25 is adapted to be positioned in the vicinity of the site by insertion through a roof of an oral cavity of the subject.

71. The apparatus according to claim 70, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a greater palatine canal of the subject.

72. The apparatus according to any one of claims 64-69, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a nose of the subject.

5 73. The apparatus according to claim 72, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a sphenopalatine foramen of the subject.

74. The apparatus according to any one of claims 64-69, wherein the support element comprises at least one mark, adapted to indicate a depth of insertion of the support element in the body.

10 75. The apparatus according to claim 74, wherein a distance of the mark from the distal end of the support element is between about 2.5 cm and about 3 cm.

76. The apparatus according to any one of claims 64-69, wherein the support element comprises a stopper, adapted to prevent insertion of the support element into the body beyond a certain depth.

15 77. The apparatus according to claim 76, wherein a distance of the stopper from the distal end of the support element is between about 2.5 cm and about 3 cm.

78. The apparatus according to any one of claims 64-69, wherein the support element is bent at one or more locations.

20 79. The apparatus according to claim 78, wherein an angle of a bend of the support element is between about 20 and about 40 degrees.

80. The apparatus according to claim 78, wherein a distance of a bend of the support element from the distal end of the support element is between about 2 cm and about 3 cm.

25 81. Apparatus for facilitating delivery of a drug to a subject, comprising:
an elongated generally rigid support element having a length of at least 1.8 cm, and having a distal end;

one or more electrodes fixed to the support element in a vicinity of the distal end thereof, and configured to be positioned in a vicinity of a site of the subject when the support element is inserted into a body of the subject, such that a portion of the support
30 element remains outside of the body, the site selected from the list consisting of: a

sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

a control unit, coupled to the support element, and adapted to:

drive the electrodes to apply an electrical current to the site, and

configure the current to induce an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of the drug across the BBB into a central nervous system (CNS) of the subject.

82. The apparatus according to claim 81, wherein the site includes the SPG of the subject, and wherein the electrodes are configured to be positioned in the vicinity of the SPG.

83. The apparatus according to claim 81, wherein the support element is substantially straight.

84. The apparatus according to claim 81, wherein the support element has a length between about 7 cm and about 13 cm.

85. The apparatus according to claim 81, wherein a portion of the support element adapted for insertion into the body has a length of between about 2.5 cm and about 3 cm.

86. The apparatus according to claim 81, wherein the control unit is adapted to configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

87. The apparatus according to any one of claims 81-86, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a roof of an oral cavity of the subject.

88. The apparatus according to claim 87, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a greater palatine canal of the subject.
89. The apparatus according to any one of claims 81-86, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a nose of the subject.
90. The apparatus according to claim 89, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a sphenopalatine foramen of the subject.
91. The apparatus according to any one of claims 81-86, wherein the support element comprises at least one mark, adapted to indicate a depth of insertion of the support element in the body.
92. The apparatus according to claim 91, wherein a distance of the mark from the distal end of the support element is between about 2.5 cm and about 3 cm.
93. The apparatus according to any one of claims 81-86, wherein the support element comprises a stopper, adapted to prevent insertion of the support element into the body beyond a certain depth.
94. The apparatus according to claim 93, wherein a distance of the stopper from the distal end of the support element is between about 2.5 cm and about 3 cm.
95. The apparatus according to any one of claims 81-86, wherein the support element is bent at one or more locations.
96. The apparatus according to claim 95, wherein an angle of a bend of the support element is between about 20 and about 40 degrees.
97. The apparatus according to claim 95, wherein a distance of a bend of the support element from the distal end of the support element is between about 2 cm and about 3 cm.
98. Apparatus for facilitating a diagnosis of a condition of a subject, comprising:
an elongated generally rigid support element having a length of at least 1.8 cm,
and having a distal end;

one or more electrodes fixed to the support element in a vicinity of the distal end thereof, and configured to be positioned in a vicinity of a site of the subject when the support element is inserted into a body of the subject, such that a portion of the support element remains outside of the body, the site selected from the list consisting of: a
5 sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the
10 subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

a control unit, coupled to the support element, and adapted to:
drive the electrodes to apply an electrical current to the site, and
configure the current to induce an increase in permeability of a blood-brain
15 barrier (BBB) of the subject sufficient to increase passage of a constituent of a central nervous system (CNS) of the subject across the BBB into a systemic blood circulation of the subject.

99. The apparatus according to claim 98, wherein the site includes the SPG of the subject, and wherein the electrodes are configured to be positioned in the vicinity of the
20 SPG.

100. The apparatus according to claim 98, wherein the support element is substantially straight.

101. The apparatus according to claim 98, wherein the support element has a length between about 7 cm and about 13 cm.

25 102. The apparatus according to claim 98, wherein a portion of the support element adapted for insertion into the body has a length of between about 2.5 cm and about 3 cm.

103. The apparatus according to claim 98, wherein the control unit is adapted to configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between
30 about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

104. The apparatus according to any one of claims 98-103, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a roof of an oral cavity of the subject.
105. The apparatus according to claim 104, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a greater palatine canal of the subject.
106. The apparatus according to any one of claims 98-103, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a nose of the subject.
107. The apparatus according to claim 106, wherein the support element is adapted to be positioned in the vicinity of the site by insertion through a sphenopalatine foramen of the subject.
108. The apparatus according to any one of claims 98-103, wherein the support element comprises at least one mark, adapted to indicate a depth of insertion of the support element in the body.
109. The apparatus according to claim 108, wherein a distance of the mark from the distal end of the support element is between about 2.5 cm and about 3 cm.
110. The apparatus according to any one of claims 98-103, wherein the support element comprises a stopper, adapted to prevent insertion of the support element into the body beyond a certain depth.
111. The apparatus according to claim 110, wherein a distance of the stopper from the distal end of the support element is between about 2.5 cm and about 3 cm.
112. The apparatus according to any one of claims 98-103, wherein the support element is bent at one or more locations.
113. The apparatus according to claim 112, wherein an angle of a bend of the support element is between about 20 and about 40 degrees.
114. The apparatus according to claim 112, wherein a distance of a bend of the support element from the distal end of the support element is between about 2 cm and about 3 cm.
115. Apparatus for facilitating a diagnosis of a condition of a subject, comprising:

a coil, adapted to be positioned in a vicinity of a site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic
5 ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

a control unit, adapted to drive the coil to generate a magnetic field in the vicinity
10 of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a diagnostic agent across the BBB into a central nervous system (CNS) of the subject.

116. The apparatus according to claim 115, wherein the site includes the SPG of the subject, and wherein the coil is adapted to be positioned in the vicinity of the SPG.

15 117. The apparatus according to claim 115, wherein the control unit is adapted to generate the magnetic field with a strength sufficient to stimulate the site, and insufficient to substantially stimulate brain tissue of the subject.

118. The apparatus according to claim 115, comprising a cooling element, adapted to prevent excessive heating of the coil.

20 119. The apparatus according to claim 115, wherein the coil comprises between about 4 and about 30 loops of wire.

120. The apparatus according to any one of claims 115-119, wherein the coil is adapted to be inserted into a nasal cavity of the subject.

25 121. The apparatus according to claim 120, wherein the coil is substantially figure-eight-shaped.

122. The apparatus according to claim 120, wherein the coil is substantially 4-leaf-shaped.

123. The apparatus according to claim 120, wherein the coil is substantially circular.

30 124. The apparatus according to claim 120, wherein the coil has a diameter of between about 3 mm and about 12 mm.

125. The apparatus according to any one of claims 115-119, wherein the coil is adapted to be placed in a vicinity of a temporomandibular joint of the subject.

126. The apparatus according to claim 125, wherein the coil has a diameter of between about 3 cm and about 12 cm.

5 127. The apparatus according to any one of claims 115-119, wherein the coil is adapted to be placed around at least a portion of a head of the subject.

128. The apparatus according to claim 127, wherein the coil has a diameter of between about 3 cm and about 12 cm.

129. Apparatus for facilitating delivery of a drug to a subject, comprising:

10 a coil, adapted to be positioned in a vicinity of a site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an
15 efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

a control unit, adapted to drive the coil to generate a magnetic field in the vicinity of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB)
20 of the subject sufficient to increase passage of the drug across the BBB into a central nervous system (CNS) of the subject.

130. The apparatus according to claim 129, wherein the site includes the SPG of the subject, and wherein the coil is adapted to be positioned in the vicinity of the SPG.

131. The apparatus according to claim 129, wherein the control unit is adapted to
25 generate the magnetic field with a strength sufficient to stimulate the site, and insufficient to substantially stimulate brain tissue of the subject.

132. The apparatus according to claim 129, comprising a cooling element, adapted to prevent excessive heating of the coil.

133. The apparatus according to claim 129, wherein the coil comprises between about
30 4 and about 30 loops of wire.

134. The apparatus according to any one of claims 129-133, wherein the coil is adapted to be inserted into a nasal cavity of the subject.
135. The apparatus according to claim 134, wherein the coil is substantially figure-eight-shaped.
- 5 136. The apparatus according to claim 134, wherein the coil is substantially 4-leaf-shaped.
137. The apparatus according to claim 134, wherein the coil is substantially circular.
138. The apparatus according to claim 134, wherein the coil has a diameter of between about 3 mm and about 12 mm.
- 10 139. The apparatus according to any one of claims 129-133, wherein the coil is adapted to be placed in a vicinity of a temporomandibular joint of the subject.
140. The apparatus according to claim 139, wherein the coil has a diameter of between about 3 cm and about 12 cm.
141. The apparatus according to any one of claims 129-133, wherein the coil is
15 adapted to be placed around at least a portion of a head of the subject.
142. The apparatus according to claim 141, wherein the coil has a diameter of between about 3 cm and about 12 cm.
143. Apparatus for facilitating a diagnosis of a condition of a subject, comprising:
a coil, adapted to be positioned in a vicinity of a site selected from the list
20 consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the
25 subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and
a control unit, adapted to drive the coil to generate a magnetic field in the vicinity
of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB)
of the subject sufficient to increase passage of a constituent of a central nervous system
30 (CNS) of the subject across the BBB into a systemic blood circulation of the subject.

144. The apparatus according to claim 143, wherein the site includes the SPG of the subject, and wherein the coil is adapted to be positioned in the vicinity of the SPG.
145. The apparatus according to claim 143, wherein the control unit is adapted to generate the magnetic field with a strength sufficient to stimulate the site, and
5 insufficient to substantially stimulate brain tissue of the subject.
146. The apparatus according to claim 143, comprising a cooling element, adapted to prevent excessive heating of the coil.
147. The apparatus according to claim 143, wherein the coil comprises between about 4 and about 30 loops of wire.
- 10 148. The apparatus according to any one of claims 143-147, wherein the coil is adapted to be inserted into a nasal cavity of the subject.
149. The apparatus according to claim 148, wherein the coil is substantially figure-eight-shaped.
150. The apparatus according to claim 148, wherein the coil is substantially 4-leaf-
15 shaped.
151. The apparatus according to claim 148, wherein the coil is substantially circular.
152. The apparatus according to claim 151, wherein the coil has a diameter of between about 3 mm and about 12 mm.
153. The apparatus according to any one of claims 143-147, wherein the coil is
20 adapted to be placed in a vicinity of a temporomandibular joint of the subject.
154. The apparatus according to claim 153, wherein the coil has a diameter of between about 3 cm and about 12 cm.
155. The apparatus according to any one of claims 143-147, wherein the coil is adapted to be placed around at least a portion of a head of the subject.
- 25 156. The apparatus according to claim 155, wherein the coil has a diameter of between about 3 cm and about 12 cm.
157. Apparatus for application to a subject, comprising:
an elongated support element having a length of between about 1.8 cm and about 4 cm, and having a proximal end and a distal end;

one or more electrodes fixed to the support element in a vicinity of the distal end thereof; and

a control unit, coupled to the support element in a vicinity of the proximal end thereof, and comprising a battery, the control unit adapted to:

- 5 drive the electrodes to apply an electrical current to tissue of the subject, and
 configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1
10 second and about 2 minutes.

158. The apparatus according to claim 157, wherein the tissue is selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic
15 ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject, and wherein the control unit is adapted to drive the electrodes to apply the current to the selected tissue.

20 159. The apparatus according to claim 157, comprising an oral appliance, coupled to the support element, and shaped so as to define a surface that fits closely to a roof of an oral cavity.

160. The apparatus according to claim 157, wherein the support element has a length of between about 1.8 cm and about 3 cm.

25 161. The apparatus according to claim 157, wherein the control unit has a volume, including the battery, of less than about 3 cm³.

162. The apparatus according to any one of claims 157-161, wherein the control unit is adapted to apply the current having on periods of between about 60 seconds and about 105 seconds, and off periods of between about 30 seconds and 90 seconds.

163. The apparatus according to claim 162, wherein the control unit is adapted to apply the current having on periods of about 90 seconds, and off periods of about 60 seconds.

164. Apparatus for application to a subject, comprising:

5 an elongated support element having a length of between about 1.8 cm and about 4 cm, and having a proximal end and a distal end;

 one or more electrodes fixed to the support element in a vicinity of the distal end thereof;

 a receiver, fixed to the support element in a vicinity of the proximal end thereof;

10 and

 a control unit, adapted to be coupled to the receiver, and adapted to:

 drive the electrodes to apply an electrical current to tissue of the subject, and

 configure the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of
15 between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

165. The apparatus according to claim 164, wherein the tissue is selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a
20 communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject,
25 and a lesser deep petrosal nerve of the subject, and wherein the control unit is adapted to drive the electrodes to apply the current to the selected tissue.

166. The apparatus according to claim 164, wherein the support element has a length of between about 1.8 cm and about 3 cm.

167. The apparatus according to claim 164, wherein the receiver comprises an
30 electrical contact site, and wherein the control unit is adapted to be coupled to the receiver by being brought into physical contact with the electrical contact site.

168. The apparatus according to any one of claims 164-167, wherein the receiver comprises a transducer, and wherein the control unit comprises a wireless transmitter, which is adapted to couple the control unit to the receiver via wireless electromagnetic communication with the transducer.

5 169. The apparatus according to claim 168, wherein the transducer comprises a coil.

170. The apparatus according to claim 168, wherein the control unit is adapted to be positioned outside of a head of the subject during operation.

171. The apparatus according to any one of claims 164-167, wherein the control unit is adapted to be positioned inside an oral cavity of the subject.

10 172. The apparatus according to claim 171, comprising an oral appliance, adapted to be fixed to the control unit, and shaped so as to define a surface that fits closely to a roof of the oral cavity.

173. The apparatus according to any one of claims 164-167, wherein the receiver has a volume of less than about 0.8 cm^3 .

15 174. The apparatus according to claim 173, wherein the receiver has a volume of less than about 0.15 cm^3 .

175. The apparatus according to any one of claims 164-167, wherein the control unit is adapted to apply the current having on periods of between about 60 seconds and about 105 seconds, and off periods of between about 30 seconds and 90 seconds.

20 176. The apparatus according to claim 175, wherein the control unit is adapted to apply the current having on periods of about 90 seconds, and off periods of about 60 seconds.

177. Apparatus for application to a subject, comprising:

an ENT endoscope, having at least one working channel;

25 at least one electrode, adapted to be passed through the working channel, and positioned in a vicinity of tissue of the subject; and

a control unit, coupled to the electrode, and adapted to drive the electrode to apply a non-ablating electrical signal to the tissue.

178. The apparatus according to claim 177, wherein the control unit is adapted to
30 configure the signal to have a pulse frequency of between about 10 Hz and about 50 Hz,

an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

- 5 179. The apparatus according to claim 177, wherein the tissue is selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an
10 efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject, and wherein the control unit is adapted to drive the electrode to apply the signal to the selected tissue.

180. The apparatus according to any one of claims 177-179, wherein the ENT
15 endoscope comprises a side-viewing scope having a viewing angle of between about 30 and about 120 degrees relative to a longitudinal axis of the endoscope.

181. The apparatus according to claim 180, wherein the electrode is adapted to be positioned so as to be viewable by the side-viewing scope.

182. Apparatus for modifying a property of a brain of a subject, comprising:
20 at least one electrode, adapted to be positioned in a vicinity of a mucous membrane of a palate of an oral cavity of the subject; and
a control unit, adapted to drive the electrode to apply an electrical current to the mucous membrane, and to configure the current to be capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject.

- 25 183. The apparatus according to claim 182, wherein the control unit is adapted to configure the current to have a magnitude sufficient to activate a sphenopalatine ganglion (SPG) of the subject via nerve fibers in physical contact with the mucous membrane.

184. The apparatus according to claim 182, wherein the control unit is adapted to
30 configure the current to increase the permeability of the BBB to a magnitude sufficient to treat a condition of the subject.

185. The apparatus according to claim 182, wherein the control unit is adapted to configure the current to increase the permeability of the BBB to a magnitude sufficient to perform a diagnosis of a condition of the subject.

186. Apparatus for modifying a property of a brain of a subject, comprising:

5 at least one electrode, adapted to be positioned in a vicinity of a mucous membrane of a palate of an oral cavity of the subject; and

 a control unit, adapted to drive the electrode to apply an electrical current to the mucous membrane, and to configure the current to be capable of inducing an increase in cerebral blood flow (CBF) of the subject.

10 187. The apparatus according to claim 186, wherein the control unit is adapted to configure the current to have a magnitude sufficient to activate a sphenopalatine ganglion (SPG) of the subject via nerve fibers in physical contact with the mucous membrane.

15 188. The apparatus according to claim 186, wherein the control unit is adapted to configure the current to increase the CBF to a magnitude sufficient to treat a condition of the subject.

189. A method for facilitating a diagnosis of a condition of a subject, comprising:

 positioning at least one electrode at at least one site of the subject for less than about 3 hours, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject,
25 a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject;

 applying an electrical current to the site of the subject; and

 configuring the current to induce an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a diagnostic agent across
30 the BBB into a central nervous system (CNS) of the subject.

190. The method according to claim 189, wherein the site includes the SPG of the subject, and wherein positioning the at least one electrode comprises positioning the at least one electrode at the SPG.

191. The method according to claim 189, wherein positioning the at least one
5 electrode comprises inserting the at least one electrode between about 2.5 cm and about 3 cm into a body of the subject.

192. The method according to claim 189, wherein configuring the current comprises configuring the current to have a pulse frequency of between about 10 Hz and about 50 Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between
10 about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

193. The method according to any one of claims 189-192, wherein positioning the at least one electrode comprises inserting the at least one electrode through a roof of an
15 oral cavity of the subject.

194. The method according to claim 193, wherein inserting the at least one electrode through the roof of the oral cavity comprises inserting the at least one electrode through a greater palatine canal of the subject.

195. The method according to any one of claims 189-192, wherein positioning the at
20 least one electrode comprises inserting the at least one electrode through a nose of the subject.

196. The method according to claim 195, wherein inserting the at least one electrode through the nose comprises inserting the at least one electrode through a sphenopalatine foramen of the subject.

25 197. The method according to any one of claims 189-192, wherein positioning the at least one electrode comprises determining a depth of insertion of the at least one electrode in a body of the subject with reference to at least one mark on the at least one electrode.

198. The method according to any one of claims 189-192, wherein positioning the
30 electrode comprises:

applying the electrical current to the site;

observing one or more physiological responses of the subject to the current; and
verifying desired placement of the electrode responsive to the observation.

199. A method for facilitating a diagnosis of a condition of a subject, comprising:
positioning at least one electrode at at least one site of the subject for less than
5 about 3 hours, the site selected from the list consisting of: a sphenopalatine ganglion
(SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the
subject, a sphenopalatine nerve of the subject, a communicating branch between a
maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent
fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic
10 ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject,
a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the
subject; and
applying an electrical current to the site of the subject; and
configuring the current to induce an increase in permeability of a blood-brain
15 barrier (BBB) of the subject sufficient to increase passage of a constituent of a central
nervous system (CNS) of the subject across the BBB into a systemic blood circulation of
the subject.
200. The method according to claim 199, wherein the site includes the SPG of the
subject, and wherein positioning the at least one electrode comprises positioning the at
20 least one electrode at the SPG.
201. The method according to claim 199, wherein positioning the at least one
electrode comprises inserting the at least one electrode between about 2.5 cm and about
3 cm into a body of the subject.
202. The method according to claim 199, wherein configuring the current comprises
25 configuring the current to have a pulse frequency of between about 10 Hz and about 50
Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between
about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of
between about 1 second and about 2 minutes, and off periods of between about 1 second
and about 2 minutes.

203. The method according to claim 199, wherein positioning the at least one electrode comprises determining a depth of insertion of the at least one electrode in a body of the subject with reference to at least one mark on the at least one electrode.

204. The method according to claim 199, comprising measuring a concentration of the constituent in the systemic blood circulation.

205. The method according to claim 199, wherein positioning the electrode comprises:

applying the electrical current to the site;

observing one or more physiological responses of the subject to the current; and

verifying desired placement of the electrode responsive to the observation.

206. The method according to any one of claims 199-205, wherein positioning the at least one electrode comprises inserting the at least one electrode through a roof of an oral cavity of the subject.

207. The method according to claim 206, wherein inserting the at least one electrode through the roof of the oral cavity comprises inserting the at least one electrode through a greater palatine canal of the subject.

208. The method according to any one of claims 199-205, wherein positioning the at least one electrode comprises inserting the at least one electrode through a nose of the subject.

209. The method according to claim 208, wherein inserting the at least one electrode through the nose comprises inserting the at least one electrode through a sphenopalatine foramen of the subject.

210. A method for facilitating a diagnosis of a condition of a subject, comprising:

selecting a site from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject; and

generating a magnetic field in the vicinity of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to increase passage of a diagnostic agent across the BBB into a central nervous system (CNS) of the subject.

5 211. The method according to claim 210, wherein the site includes the SPG of the subject, and wherein generating the magnetic field comprises generating the magnetic field in the vicinity of the SPG.

212. The method according to claim 210, wherein generating the magnetic field comprises generating the magnetic field with a strength sufficient to stimulate the site,
10 and insufficient to substantially stimulate brain tissue of the subject.

213. The method according to claim 210, generating the magnetic field comprises cooling the vicinity of the site.

214. The method according to claim 210, wherein generating the magnetic field comprises generating the magnetic field from within a nasal cavity of the subject.

15 215. The method according to claim 210, wherein generating the magnetic field comprises generating the magnetic field at a vicinity of a temporomandibular joint of the subject.

216. The method according to claim 210, wherein generating the magnetic field comprises generating the magnetic field from around at least a portion of a head of the
20 subject.

217. A method for facilitating a diagnosis of a condition of a subject, comprising:

selecting a site from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary
25 nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject;
and

30 generating a magnetic field in the vicinity of the site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the subject sufficient to

increase passage of a constituent of a central nervous system (CNS) of the subject across the BBB into a systemic blood circulation of the subject.

218. The method according to claim 217, wherein the site includes the SPG of the subject, and wherein generating the magnetic field comprises generating the magnetic field in the vicinity of the SPG.

219. The method according to claim 217, wherein generating the magnetic field comprises generating the magnetic field with a strength sufficient to stimulate the site, and insufficient to substantially stimulate brain tissue of the subject.

220. The method according to claim 217, wherein generating the magnetic field comprises cooling the vicinity of the site.

221. The method according to claim 217, wherein generating the magnetic field comprises generating the magnetic field from within a nasal cavity of the subject.

222. The method according to claim 217, wherein generating the magnetic field comprises generating the magnetic field at a vicinity of a temporomandibular joint of the subject.

223. The method according to claim 217, wherein generating the magnetic field comprises generating the magnetic field from around at least a portion of a head of the subject.

224. The method according to any one of claims 217-223, comprising measuring a concentration of the constituent in the systemic blood circulation.

225. A method comprising:
inserting an ENT endoscope, having at least one working channel, into a body of a subject;
passing at least one electrode through the working channel;
positioning the electrode in a vicinity of tissue of the subject;
driving the electrode to apply a non-ablating electrical signal to the tissue; and
performing a diagnostic procedure following initiation of application of the signal.

226. The method according to claim 225, wherein driving the electrode comprises configuring the signal to have a pulse frequency of between about 10 Hz and about 50

Hz, an amplitude of between about 0.2 V and about 10 V, a pulse width of between about 50 microseconds and about 5 milliseconds, and, in alternation, on periods of between about 1 second and about 2 minutes, and off periods of between about 1 second and about 2 minutes.

5 227. The method according to claim 225, wherein the tissue is selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve and an SPG of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion of the subject, an efferent fiber going out of the otic ganglion of the subject, an infraorbital nerve of the subject, a vidian nerve of the subject, a greater superficial petrosal nerve of the subject, and a lesser deep petrosal nerve of the subject, and wherein driving the electrode comprises driving the electrode to apply the signal to the selected tissue.

10 228. The method according to any one of claims 225-227, wherein the ENT endoscope includes a side-viewing scope having a viewing angle of between about 30 and about 120 degrees relative to a longitudinal axis of the endoscope, and comprising viewing the vicinity of the tissue via the scope.

229. The method according to claim 228, wherein viewing the vicinity of the tissue comprises viewing the electrode via the scope.

20 230. A method for modifying a property of a brain of a subject, comprising:
applying to a branch of a cranial nerve V of the subject an electrical current configured to affect physiological activity of a sphenopalatine ganglion (SPG) of the subject at a level sufficient to induce an increase in permeability of a blood-brain barrier (BBB) of the subject; and

25 performing a diagnostic activity with respect to a condition of the subject, in conjunction with the increase in permeability of the BBB.

231. The method according to claim 230, comprising administering a sedative to the subject in conjunction with applying the current.

232. The method according to claim 230, comprising administering an anesthetic to
30 the subject in conjunction with applying the current.

233. The method according to claim 230, wherein applying the current comprises:

placing one or more electrodes on a surface of a face of the subject; and
driving the electrodes to apply the current to the branch of the cranial nerve V.

234. A method for modifying a property of a brain of a subject, comprising:
generating a magnetic field in the vicinity of a branch of a cranial nerve V of the
5 subject configured to affect physiological activity of a sphenopalatine ganglion (SPG) of
the subject at a level sufficient to induce an increase in permeability of a blood-brain
barrier (BBB) of the subject; and
performing a diagnostic activity with respect to a condition of the subject, in
conjunction with the increase in permeability of the BBB.
- 10 235. The method according to claim 234, comprising administering a sedative to the
subject in conjunction with generating the magnetic field.
236. The method according to claim 234, comprising administering an anesthetic to
the subject in conjunction with generating the magnetic field.
237. A method for modifying a property of a brain of a subject, comprising:
15 applying an electrical current to a mucous membrane of a palate of an oral cavity
of the subject, the current capable of inducing an increase in permeability of a blood-
brain barrier (BBB) of the subject; and
performing a diagnostic activity with respect to a condition of the subject, in
conjunction with the increase in permeability of the BBB.
- 20 238. The method according to claim 237, comprising administering a sedative to the
subject in conjunction with applying the current.
239. The method according to claim 237, comprising administering an anesthetic to
the subject in conjunction with applying the current.
240. The method according to claim 237, wherein applying the current comprises
25 configuring the current to have a magnitude sufficient to activate a sphenopalatine
ganglion (SPG) of the subject via nerve fibers in physical contact with the mucous
membrane.
241. A method for facilitating a diagnosis of a condition of a central nervous system
(CNS) of a subject, the method comprising:

stimulating at least one site of the subject by applying an electrical current to the site, the site selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between the anterior ethmoidal nerve and the SPG, a
5 communicating branch between the posterior ethmoidal nerve and the SPG, a nerve of the pterygoid canal of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve of the subject and the SPG, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital nerve of the subject, an otic
10 ganglion of the subject, an afferent fiber going into the otic ganglion, and an efferent fiber going out of the otic ganglion;

configuring the stimulation so as to cause an increase in molecular passage between the CNS and another body compartment of the subject;

taking a sample from the body compartment;

15 determining a level of a constituent of the sample; and

interpreting a low value of the level as indicative of an increased likelihood that the subject suffers from the CNS condition.

242. A method for facilitating a diagnosis of a condition of a central nervous system (CNS) of a subject, the method comprising:

20 stimulating at least one site of the subject selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between the anterior ethmoidal nerve and the SPG, a communicating branch between the posterior ethmoidal nerve and the SPG, a nerve of the pterygoid canal of the subject, a greater palatine nerve
25 of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve of the subject and the SPG, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital nerve of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion, and an efferent fiber going out of the otic ganglion;

30 configuring the stimulation so as to cause an increase in molecular passage between the CNS and another body compartment of the subject;

taking a sample from the body compartment;

determining a level of a constituent of the sample; and

interpreting a low value of the level as indicative of an increased likelihood that the subject suffers from the CNS condition.

243. The method according to claim 242, wherein stimulating comprises applying magnetic stimulation to the site.

5 244. The method according to claim 242, wherein stimulating comprises applying electromagnetic stimulation to the site.

245. The method according to claim 242, wherein stimulating comprises applying chemical stimulation to the site.

246. The method according to claim 242, wherein stimulating comprises applying
10 mechanical stimulation to the site.

247. The method according to any one of claims 241-246, comprising interpreting a high value of the level as indicative of a decreased likelihood that the subject suffers from the CNS condition.

248. The method according to any one of claims 241-246, wherein the body
15 compartment includes a systemic blood circulation of the subject, and wherein configuring the stimulation comprises configuring the stimulation so as to cause the increase in molecular passage between the CNS and the systemic blood circulation.

249. The method according to any one of claims 241-246, wherein the body
20 compartment includes plasma of the subject, and wherein configuring the stimulation comprises configuring the stimulation so as to cause the increase in molecular passage between the CNS and the plasma.

250. The method according to any one of claims 241-246, wherein the body
25 compartment includes serum of the subject, and wherein configuring the stimulation comprises configuring the stimulation so as to cause the increase in molecular passage between the CNS and the serum.

251. The method according to any one of claims 241-246, wherein the body compartment is ascites of the subject, and wherein configuring the stimulation comprises configuring the stimulation so as to cause the increase in molecular passage between the CNS and the ascites.

252. The method according to any one of claims 241-246, wherein the site includes the SPG, and wherein stimulating the site comprises stimulating the SPG.

253. The method according to any one of claims 241-246, wherein the CNS condition includes Alzheimer's disease, and wherein interpreting the low value comprises
5 interpreting the low value as indicative of the increased likelihood that the subject suffers from Alzheimer's disease.

254. The method according to claim 253, wherein the constituent includes amyloid-beta peptide, and wherein determining the level of the constituent comprises determining the level of the amyloid-beta peptide.

10 255. The method according to claim 253, wherein the constituent includes presenilin-1, and wherein determining the level of the constituent comprises determining the level of the presenilin-1.

256. A method for facilitating a diagnosis of a condition of a central nervous system (CNS) of a subject, the method comprising:

15 determining a level of a constituent of a sample taken from a body compartment of the subject other than the CNS after commencement of electrical stimulation of at least one site of the subject selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between the anterior ethmoidal
20 nerve and the SPG, a communicating branch between the posterior ethmoidal nerve and the SPG, a nerve of the pterygoid canal of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve of the subject and the SPG, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital
25 nerve of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion, and an efferent fiber going out of the otic ganglion; and

interpreting a low value of the level as indicative of an increased likelihood that the subject suffers from the CNS condition.

257. A method for facilitating a diagnosis of a condition of a central nervous system
30 (CNS) of a subject, the method comprising:

determining a level of a constituent of a sample taken from a body compartment of the subject other than the CNS after commencement of stimulation of at least one site of the subject selected from the list consisting of: a sphenopalatine ganglion (SPG) of the subject, an anterior ethmoidal nerve of the subject, a posterior ethmoidal nerve of the subject, a communicating branch between the anterior ethmoidal nerve and the SPG, a communicating branch between the posterior ethmoidal nerve and the SPG, a nerve of the pterygoid canal of the subject, a greater palatine nerve of the subject, a lesser palatine nerve of the subject, a sphenopalatine nerve of the subject, a communicating branch between a maxillary nerve of the subject and the SPG, a nasopalatine nerve of the subject, a posterior nasal nerve of the subject, an infraorbital nerve of the subject, an otic ganglion of the subject, an afferent fiber going into the otic ganglion, and an efferent fiber going out of the otic ganglion; and

interpreting a low value of the level as indicative of an increased likelihood that the subject suffers from the CNS condition.

258. The method according to claim 257, wherein determining the level after the commencement of the stimulation comprises determining the level after the commencement of magnetic stimulation of the site.

259. The method according to claim 257, wherein determining the level after the commencement of the stimulation comprises determining the level after the commencement of electromagnetic stimulation of the site.

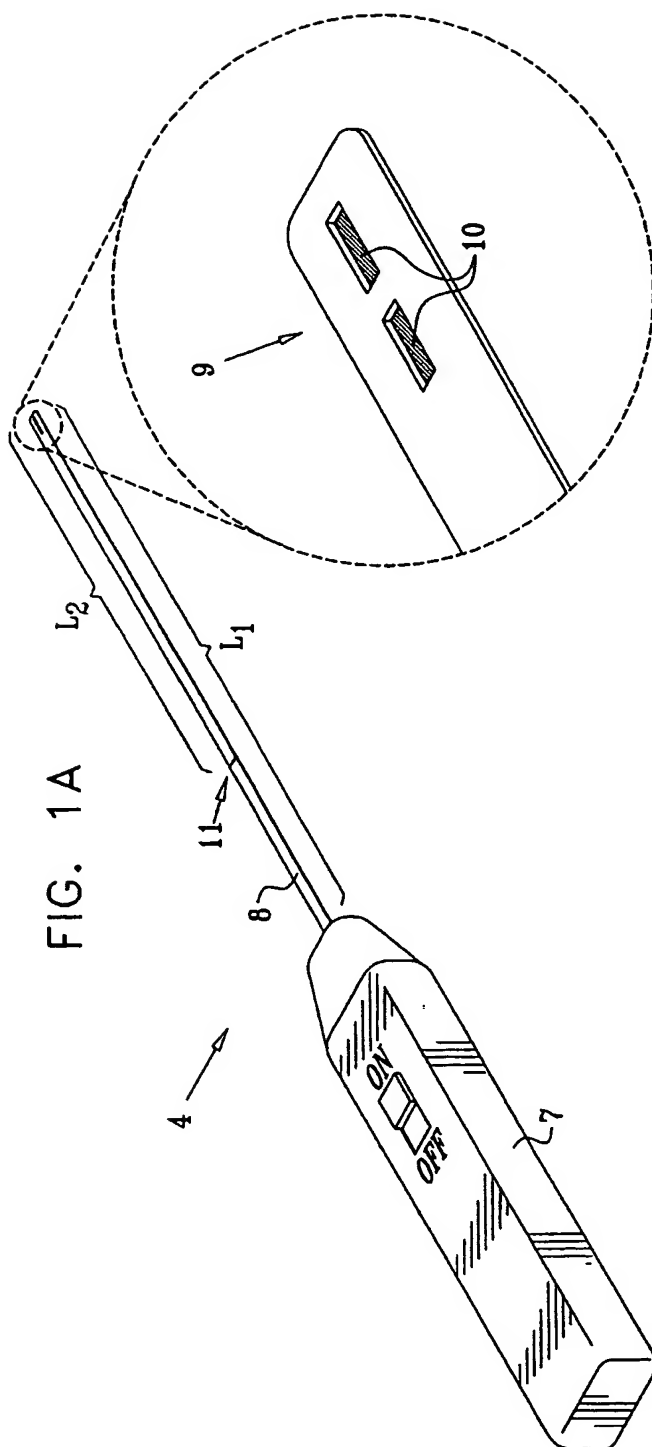
260. The method according to claim 257, wherein determining the level after the commencement of the stimulation comprises determining the level after the commencement of chemical stimulation of the site.

261. The method according to claim 257, wherein determining the level after the commencement of the stimulation comprises determining the level after the commencement of mechanical stimulation of the site.

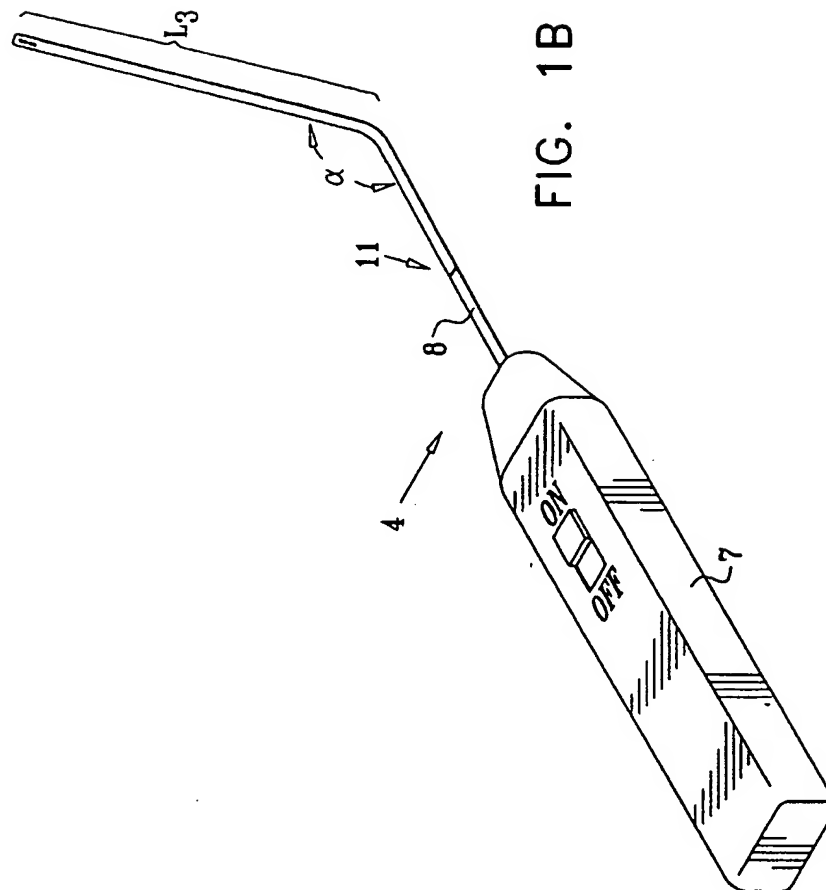
262. The method according to any one of claims 256-261, wherein the body compartment includes a systemic blood circulation of the subject, and wherein determining the level comprises determining the level of the constituent of the sample taken from the systemic blood circulation.

263. The method according to any one of claims 256-261, wherein the body compartment includes plasma of the subject, and determining the level comprises determining the level of the constituent of the sample taken from the plasma.
264. The method according to any one of claims 256-261, wherein the body
5 compartment includes serum of the subject, and determining the level comprises determining the level of the constituent of the sample taken from the serum.
265. The method according to any one of claims 256-261, wherein the body compartment is ascites of the subject, and determining the level comprises determining the level of the constituent of the sample taken from the ascites.
- 10 266. The method according to any one of claims 256-261, wherein the site includes the SPG, and wherein determining the level comprises determining the level of the constituent of the sample taken from the body compartment after the commencement of the stimulation of the SPG.
267. The method according to any one of claims 256-261, wherein the CNS condition
15 includes Alzheimer's disease, and wherein interpreting the low value comprises interpreting the low value as indicative of the increased likelihood that the subject suffers from Alzheimer's disease.
268. The method according to claim 267, wherein the constituent includes amyloid-beta peptide, and wherein determining the level of the constituent comprises determining
20 the level of the amyloid-beta peptide.
269. The method according to claim 267, wherein the constituent includes presenilin-1, and wherein determining the level of the constituent comprises determining the level of the presenilin-1.

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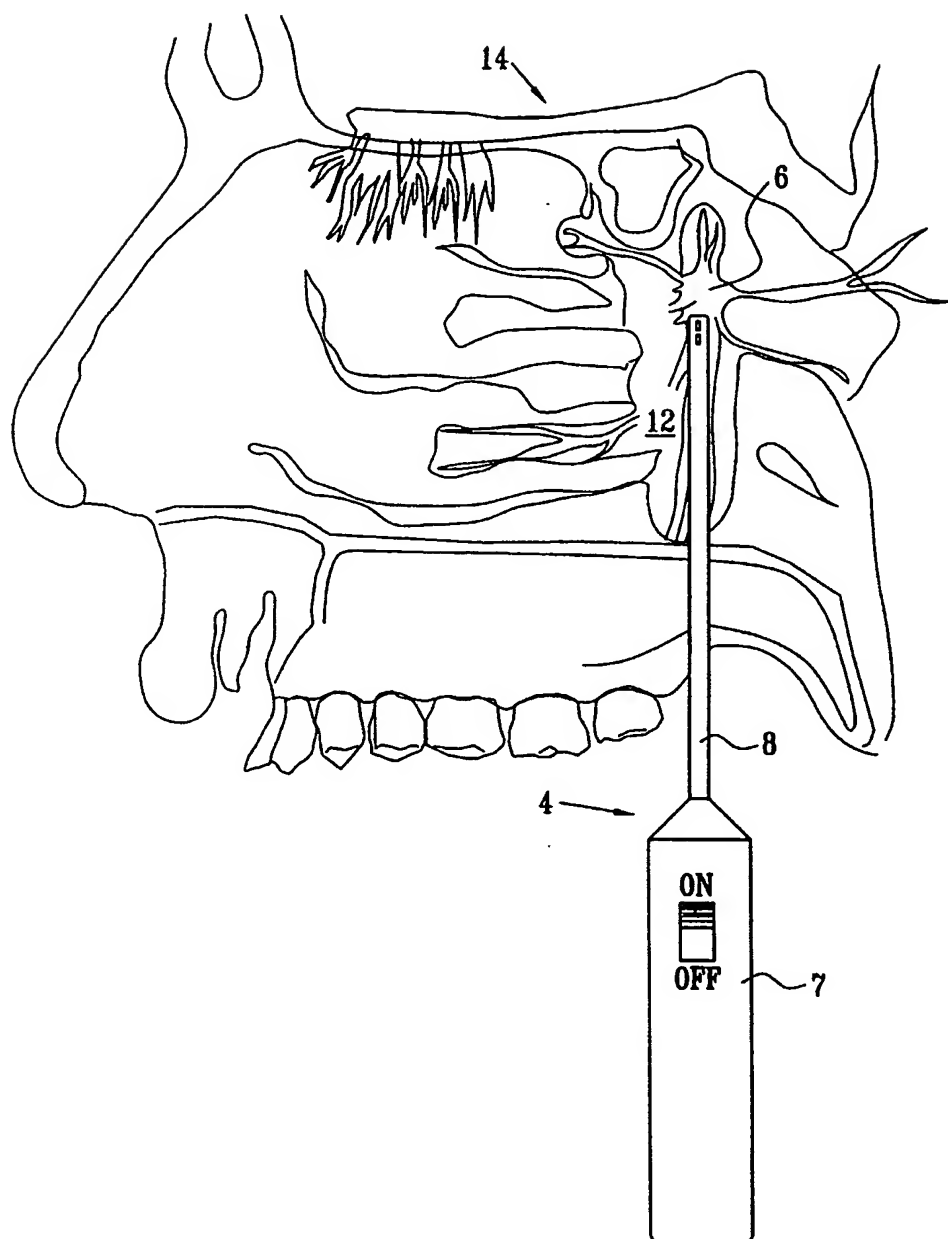


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FIG. 2A



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FIG. 2B

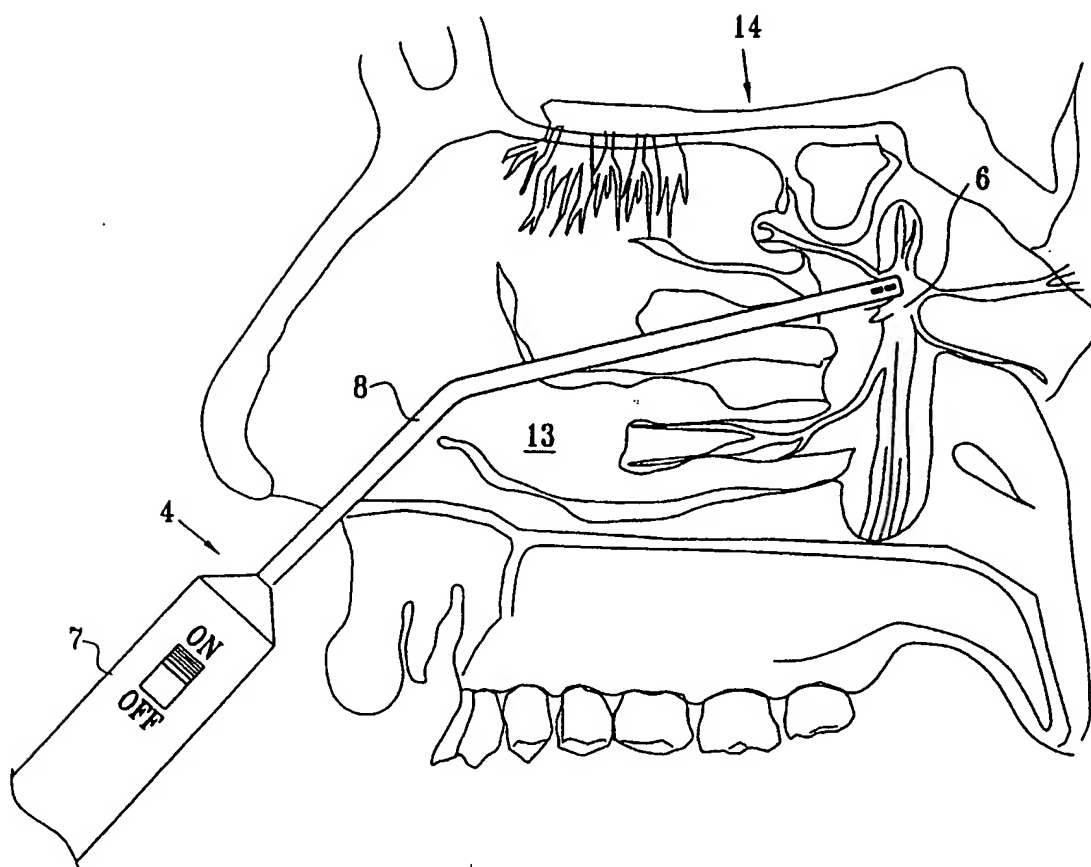
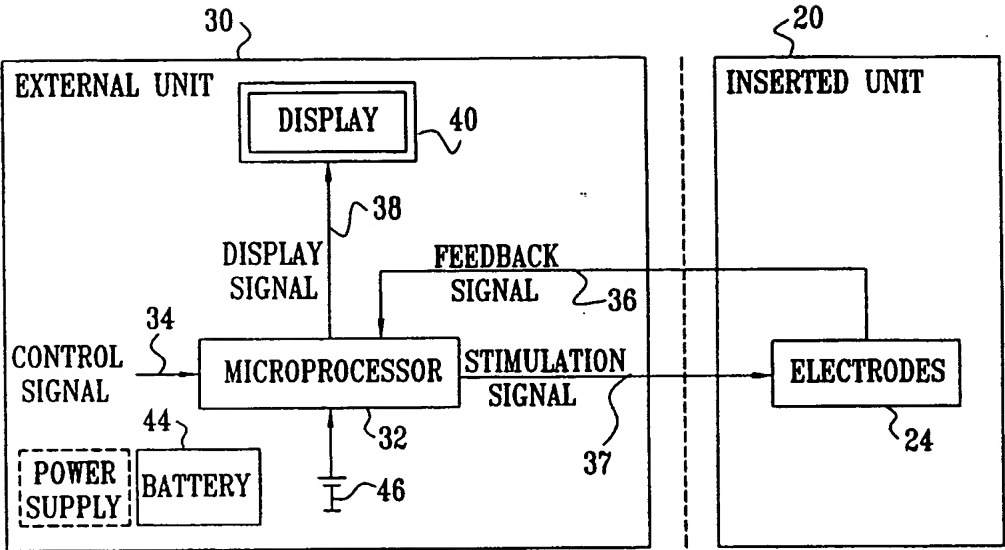


FIG. 3



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FIG. 4A

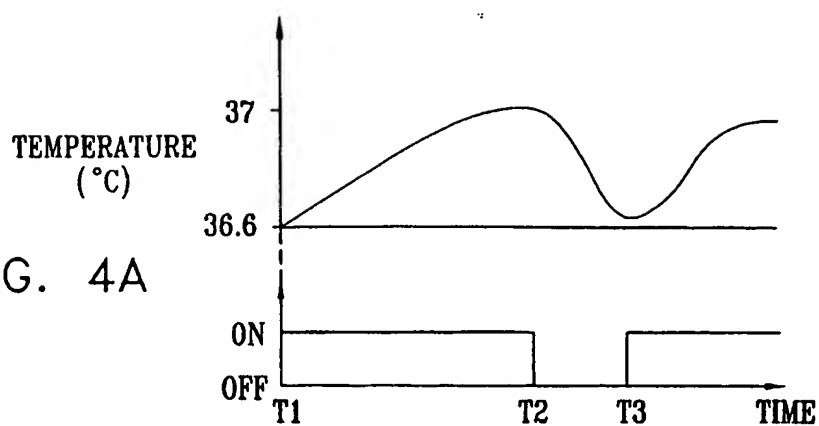


FIG. 4B

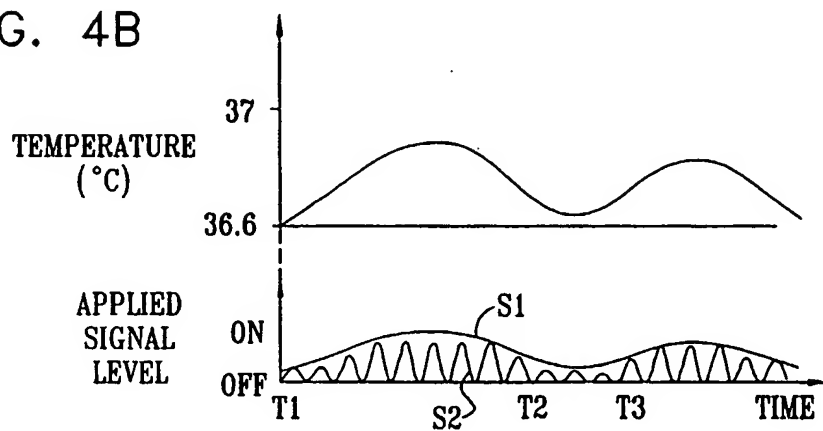
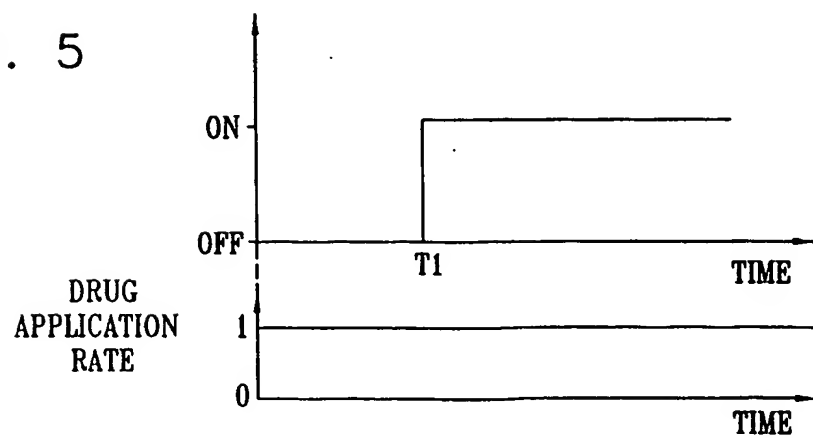
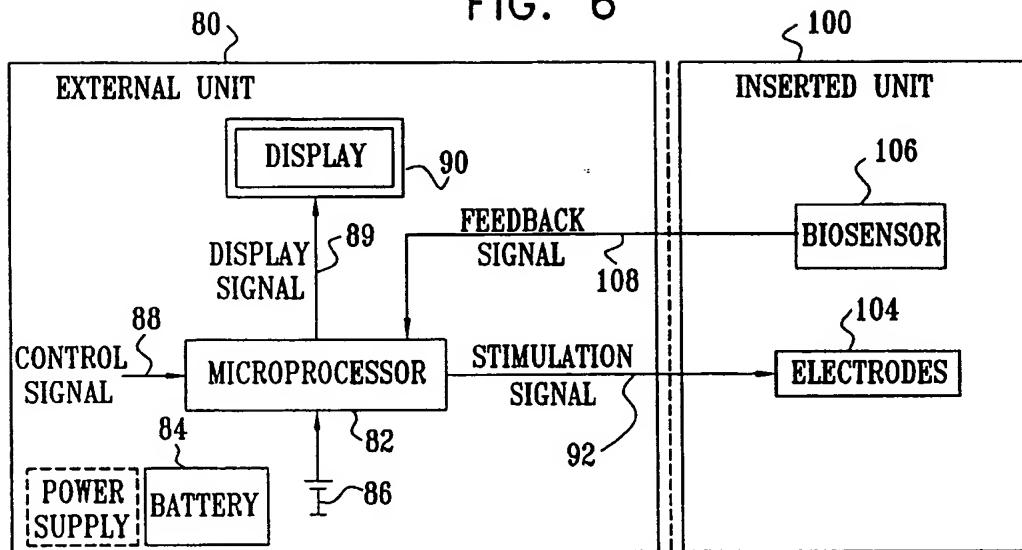


FIG. 5

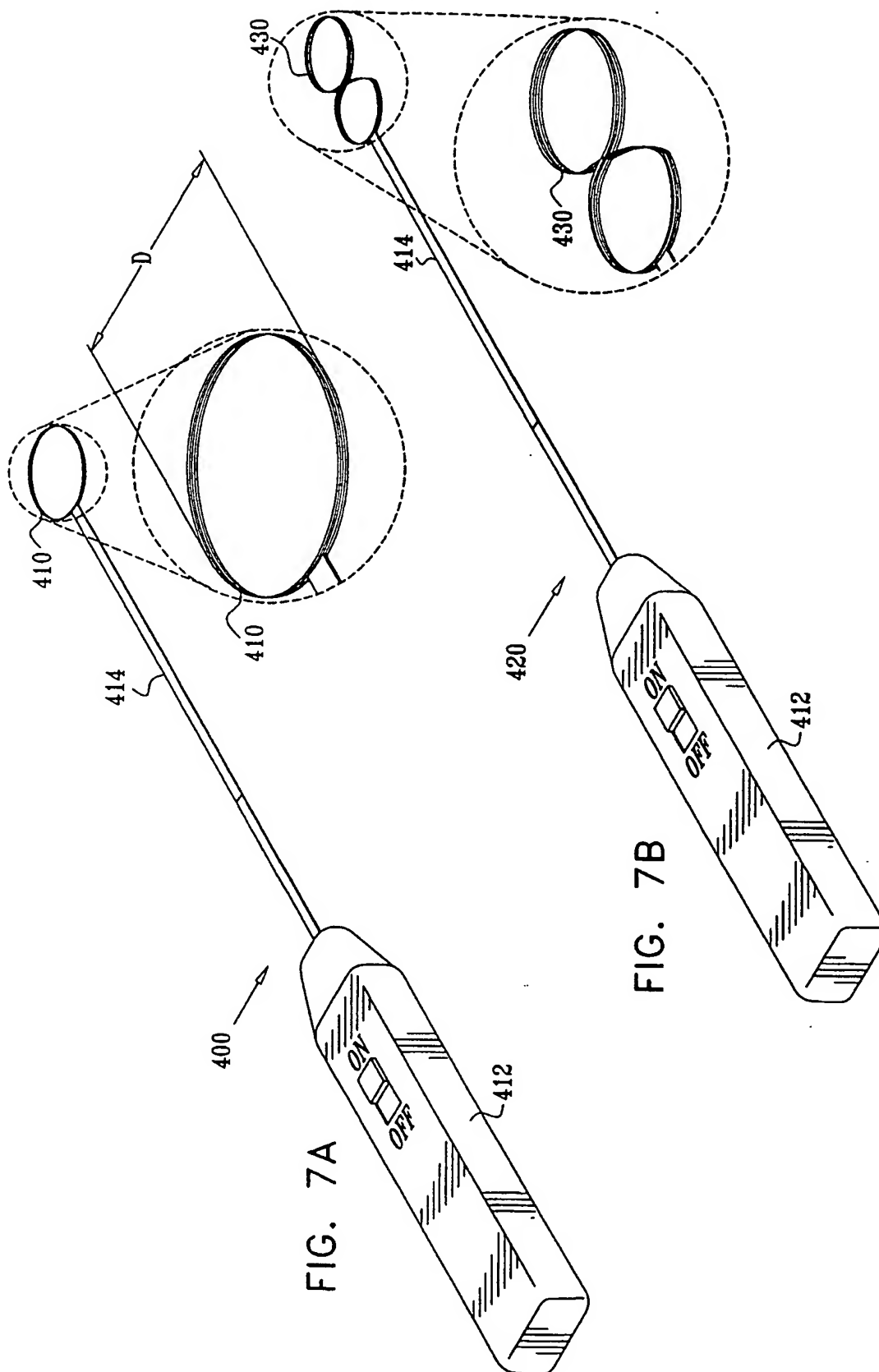


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FIG. 6



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FIG. 8A

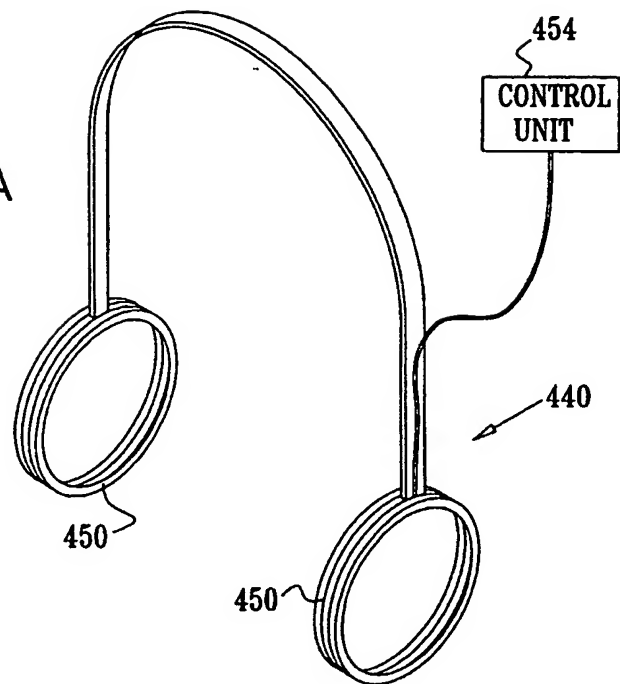
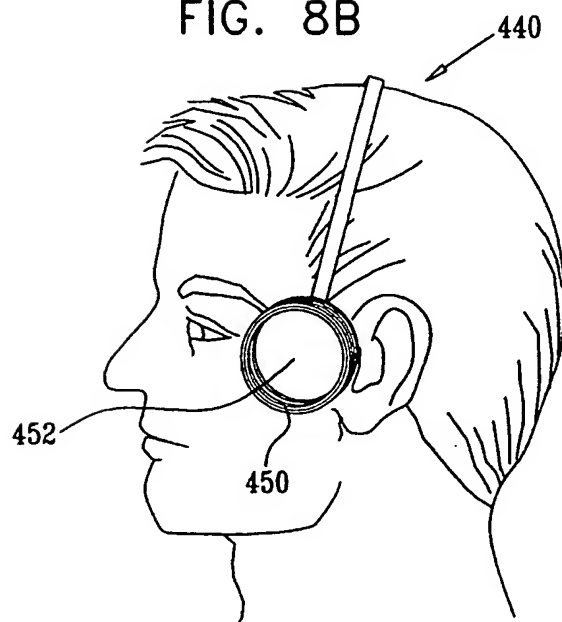


FIG. 8B



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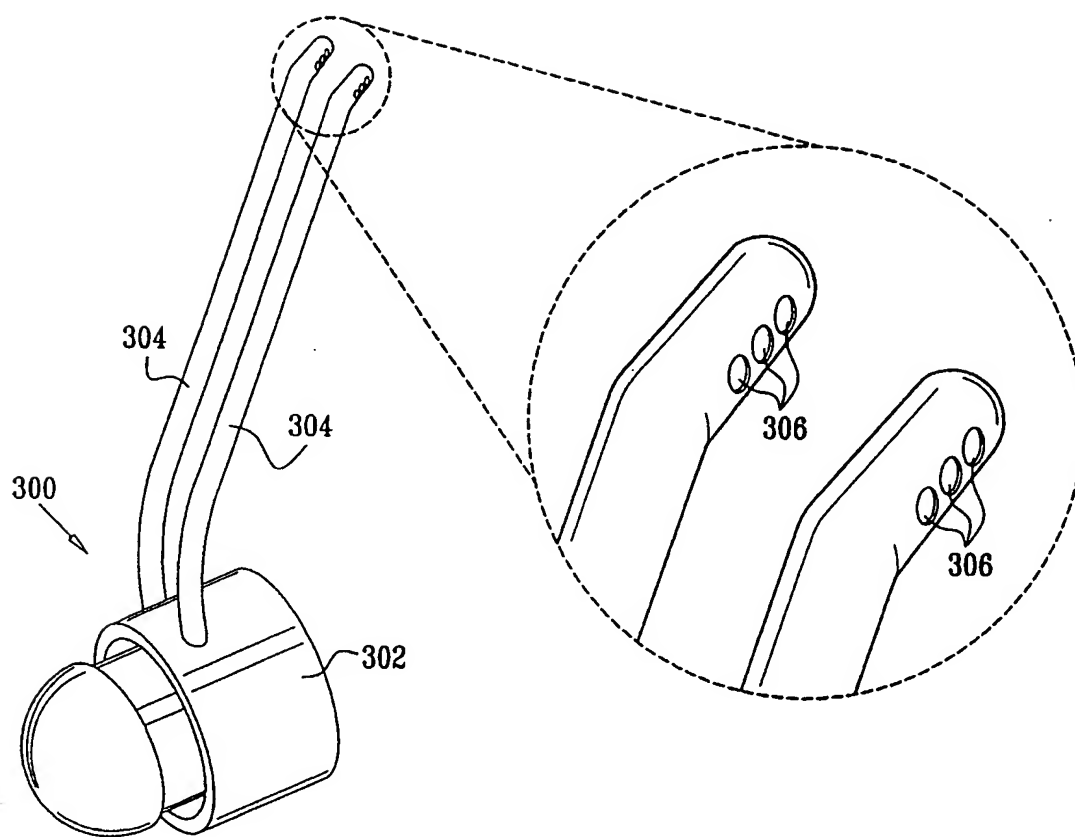





FIG. 9

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FIG. 10

 CONTROL PIG
 EXPERIMENTAL PIG 1
 EXPERIMENTAL PIG 2

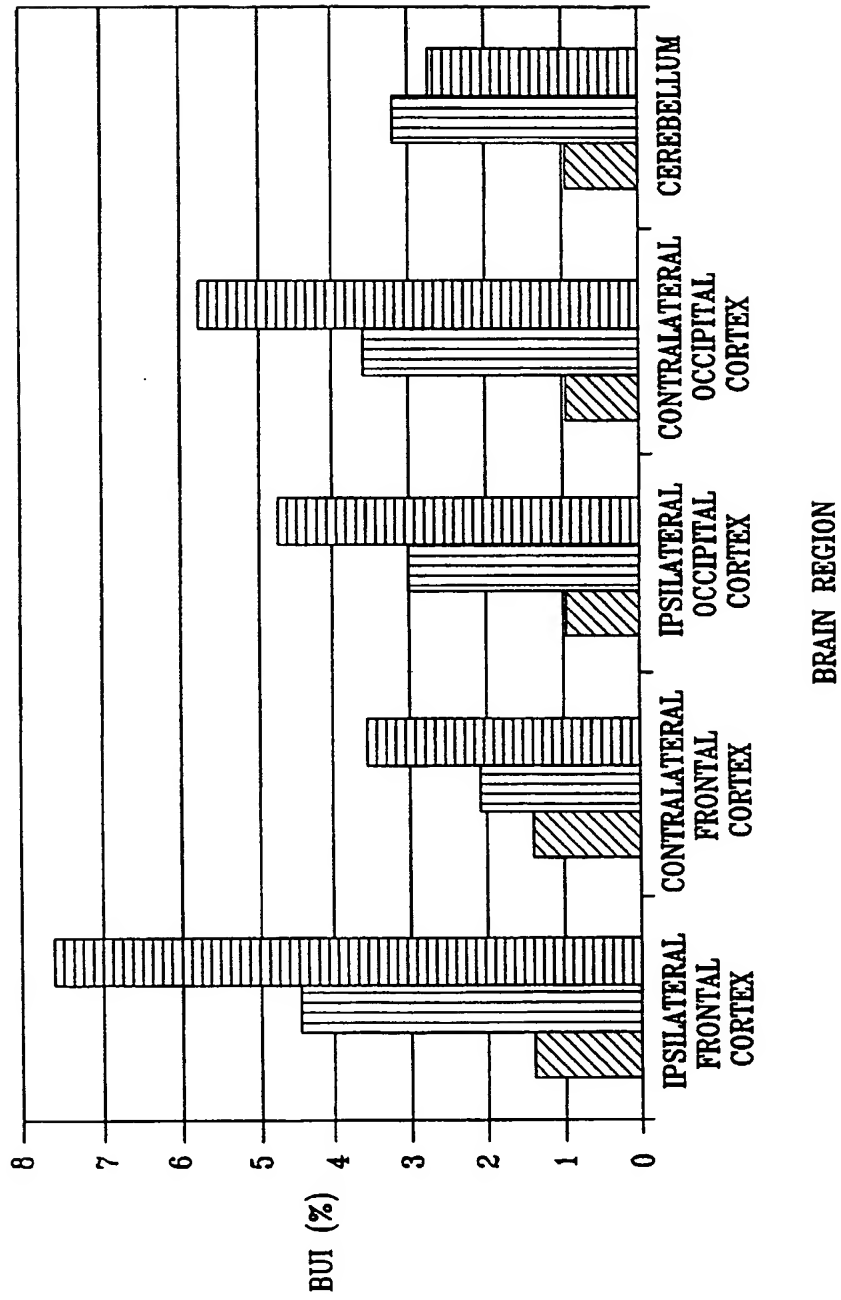
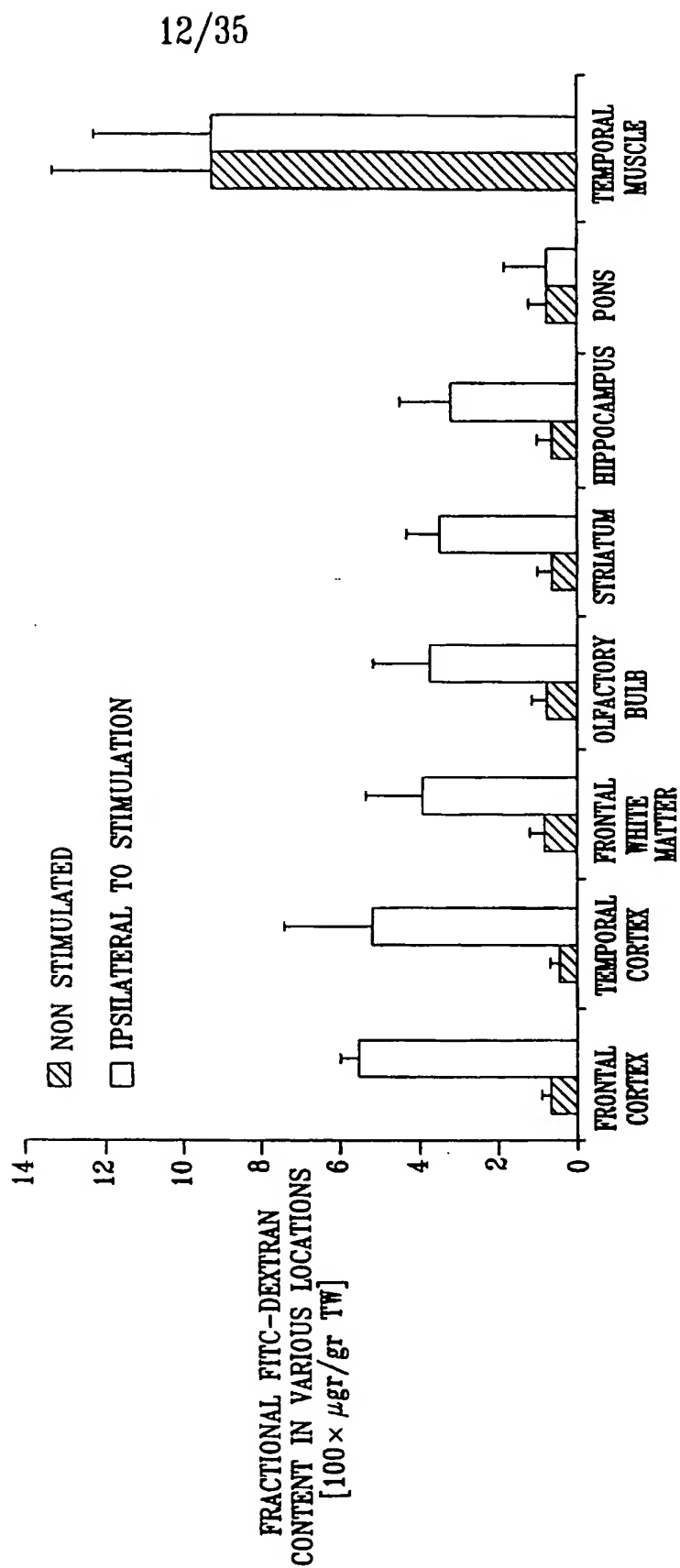


FIG. 11



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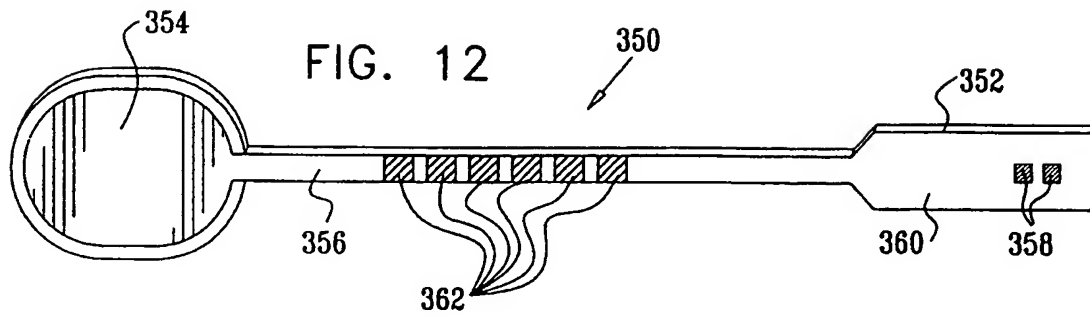


FIG. 13

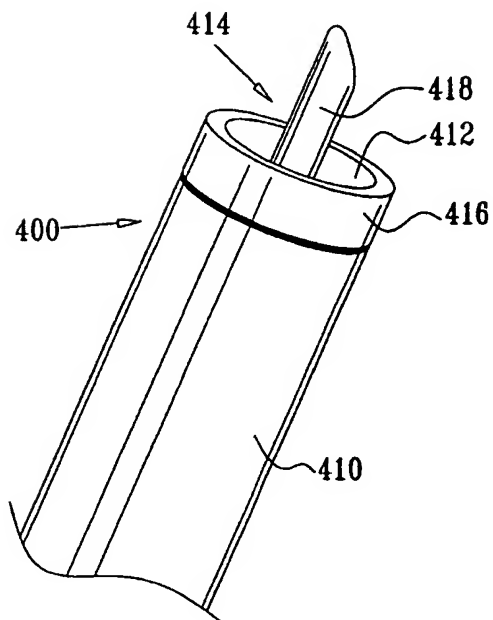
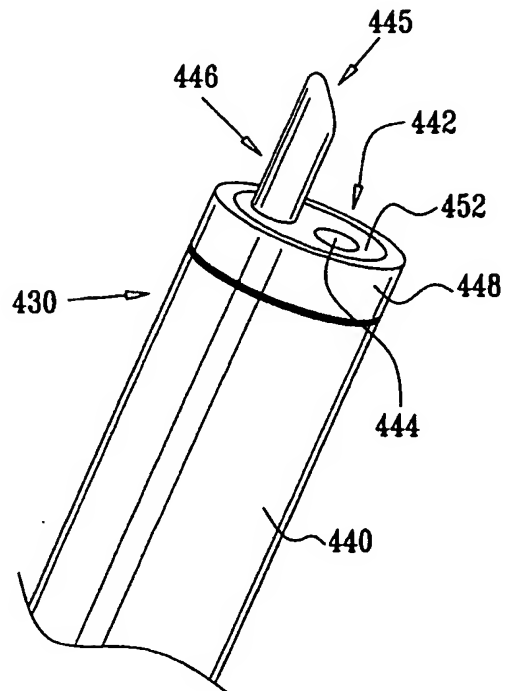
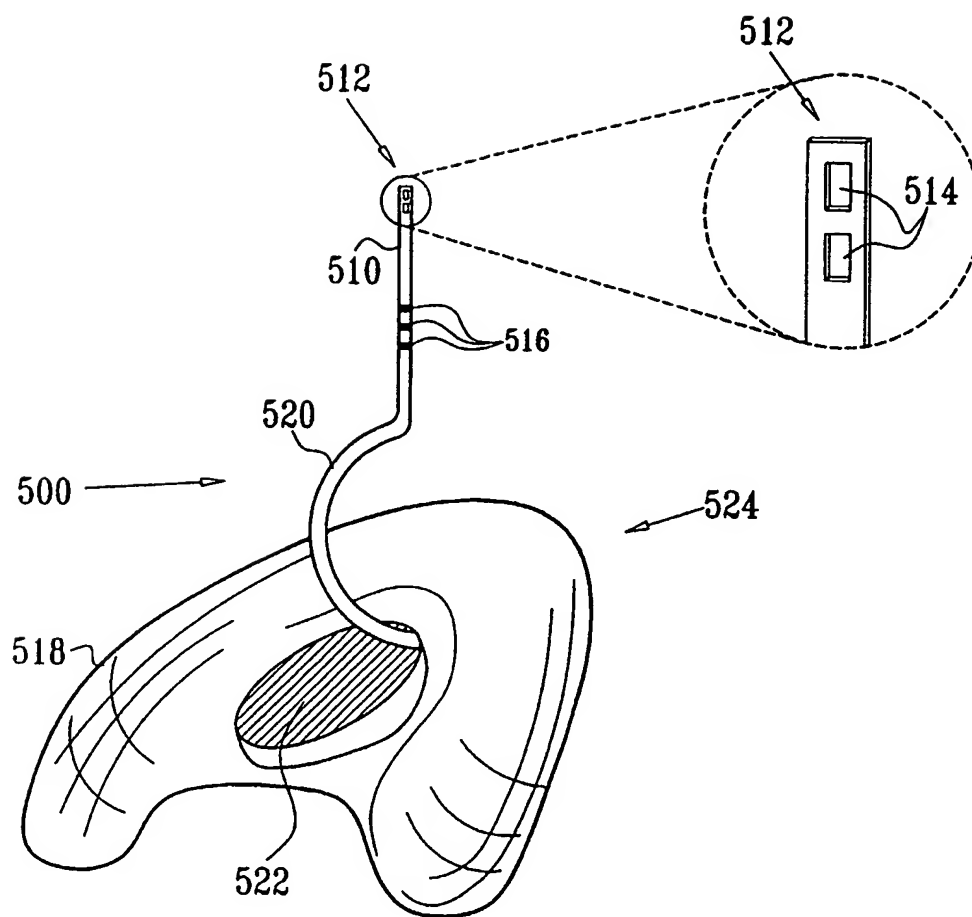


FIG. 14



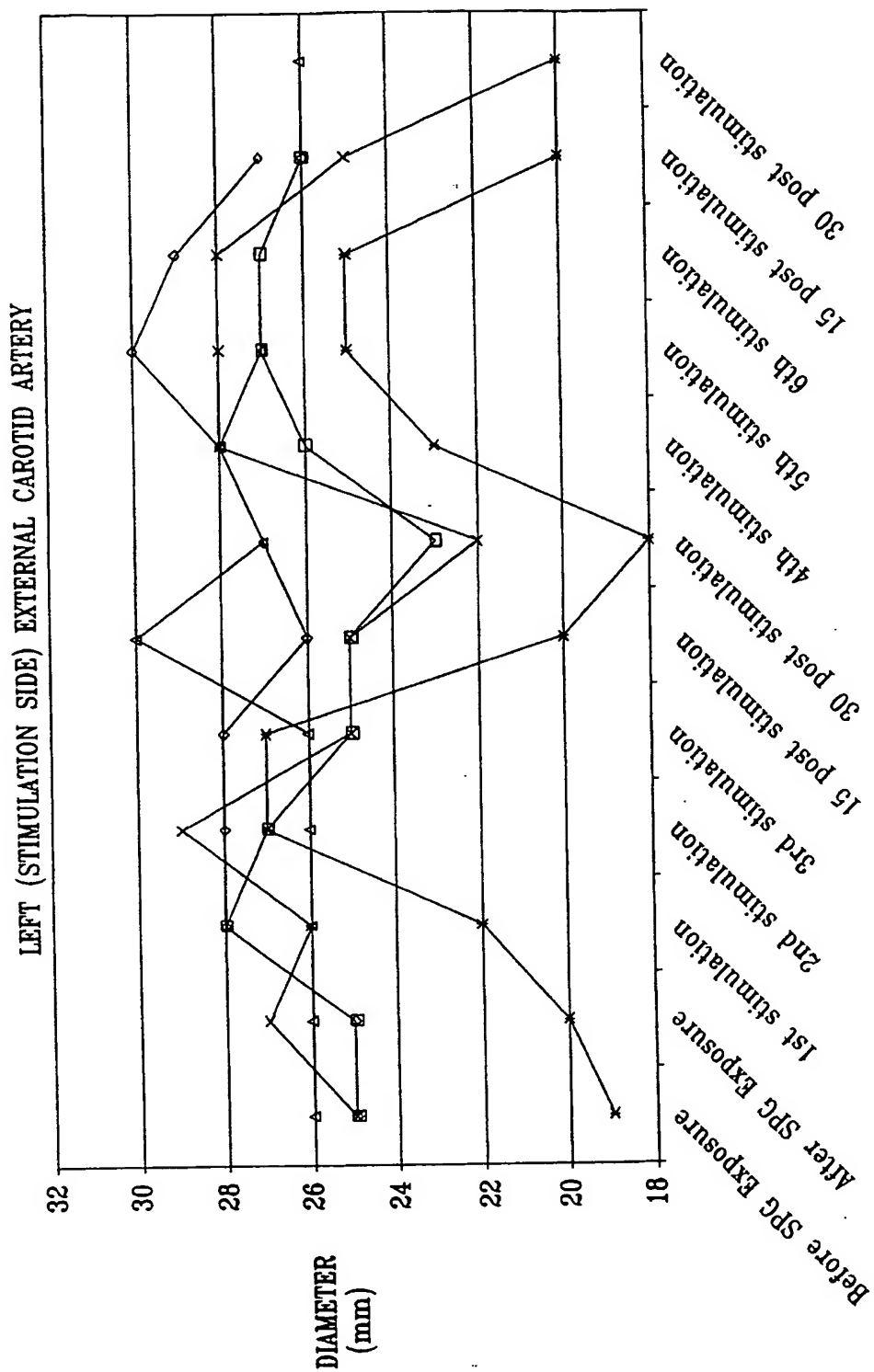
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FIG. 15



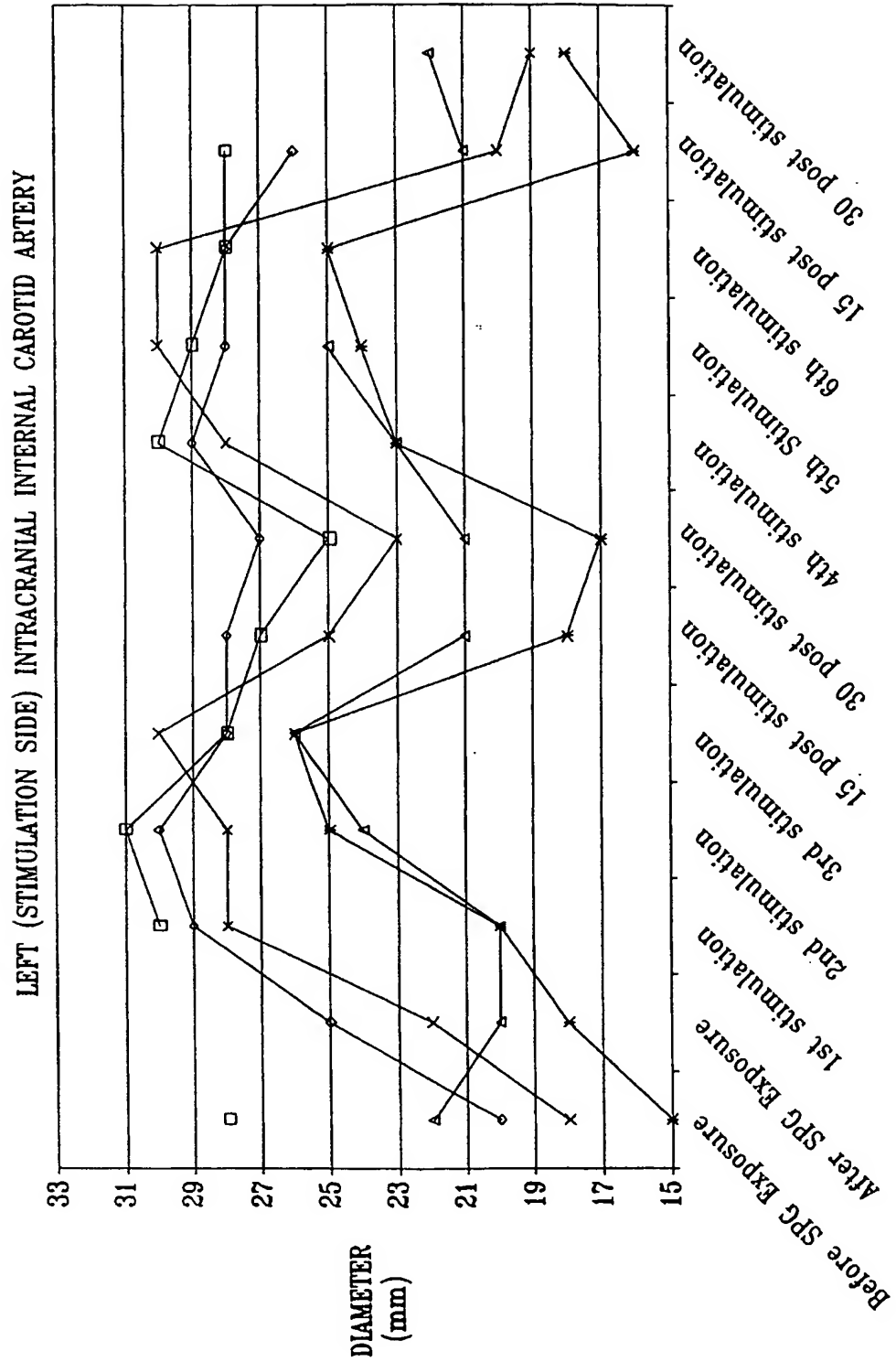
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FIG. 16A



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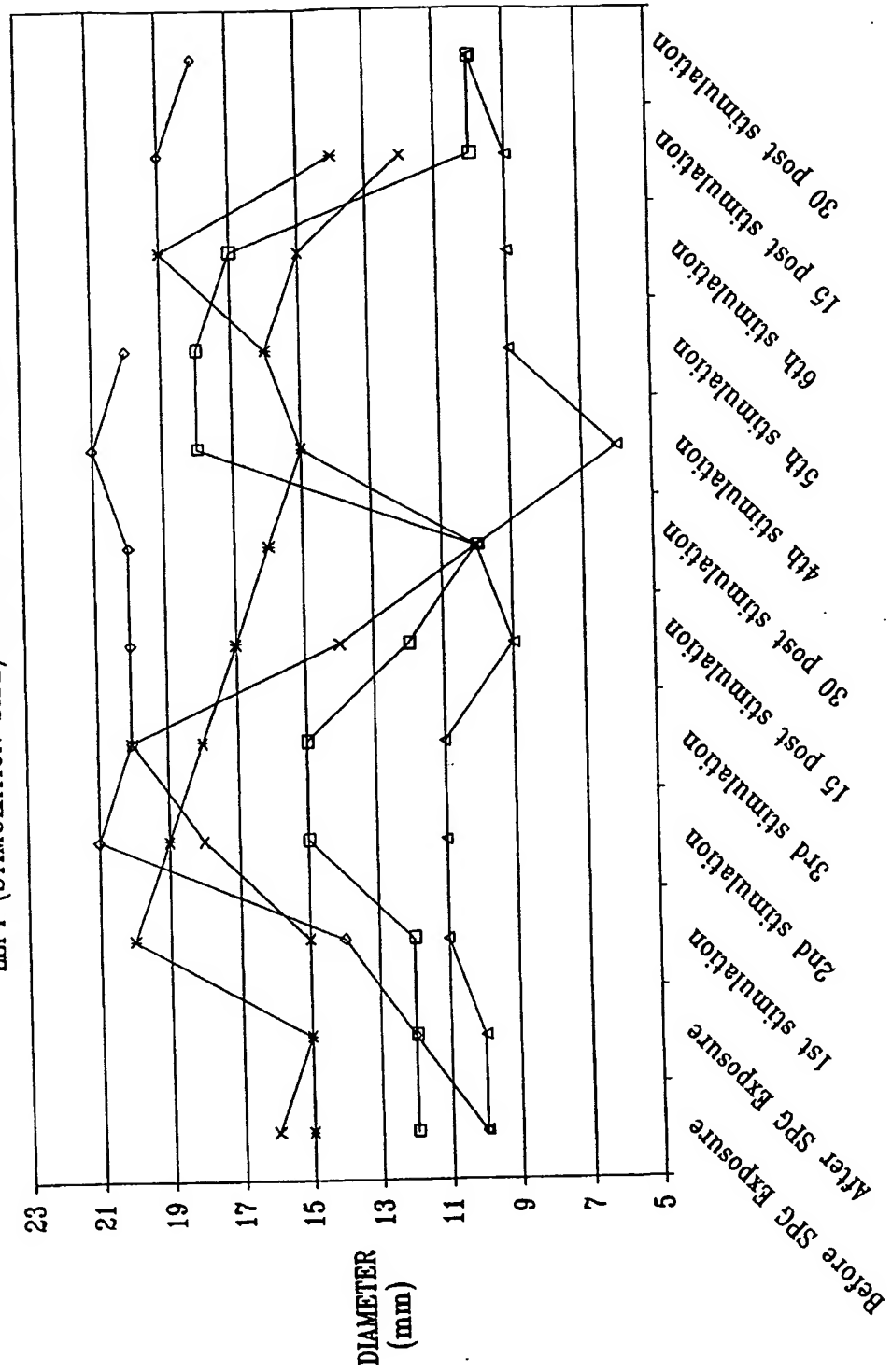
FIG. 16B



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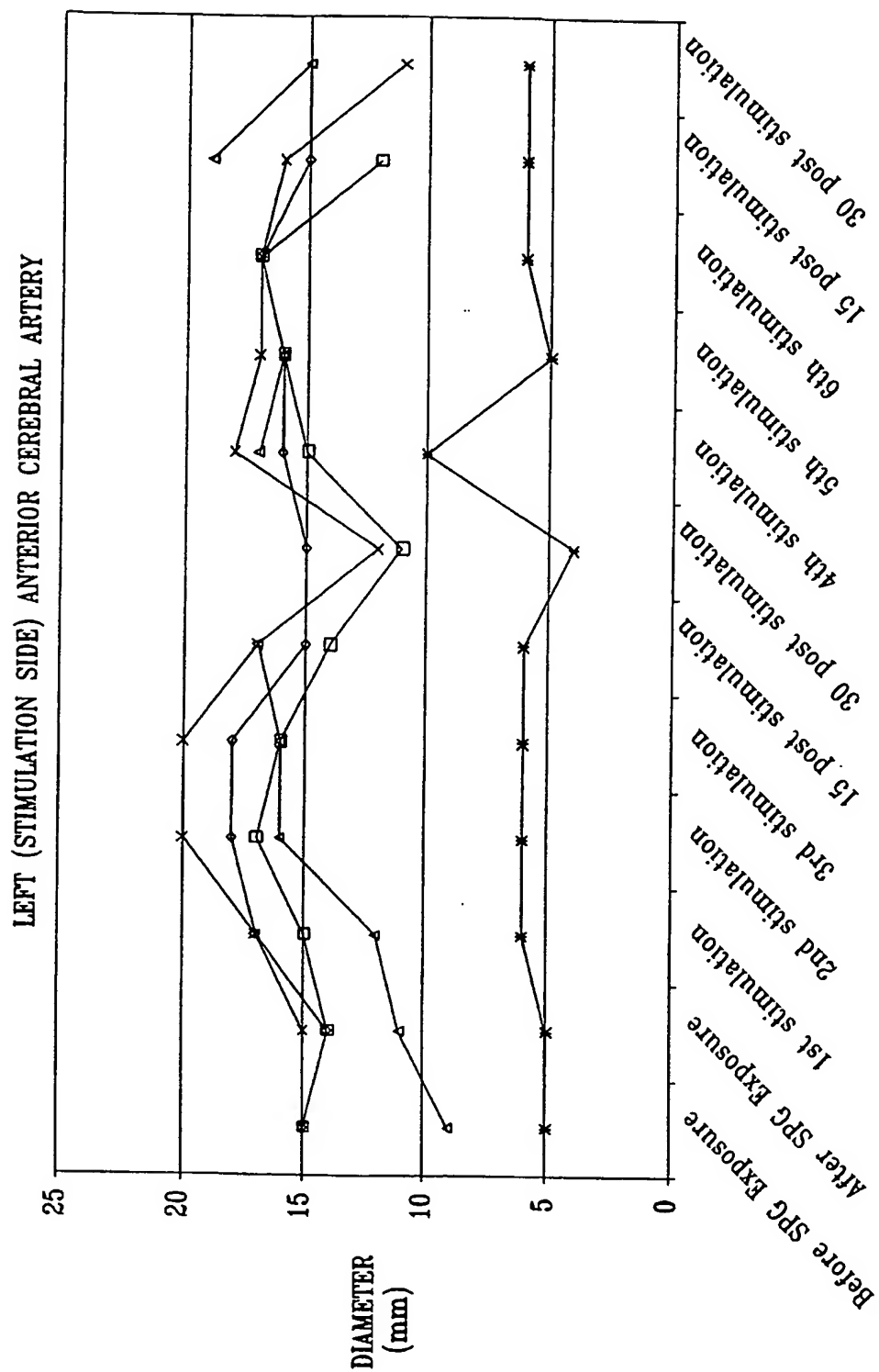
FIG. 16C

LEFT (STIMULATION SIDE) MIDDLE CEREBRAL ARTERY



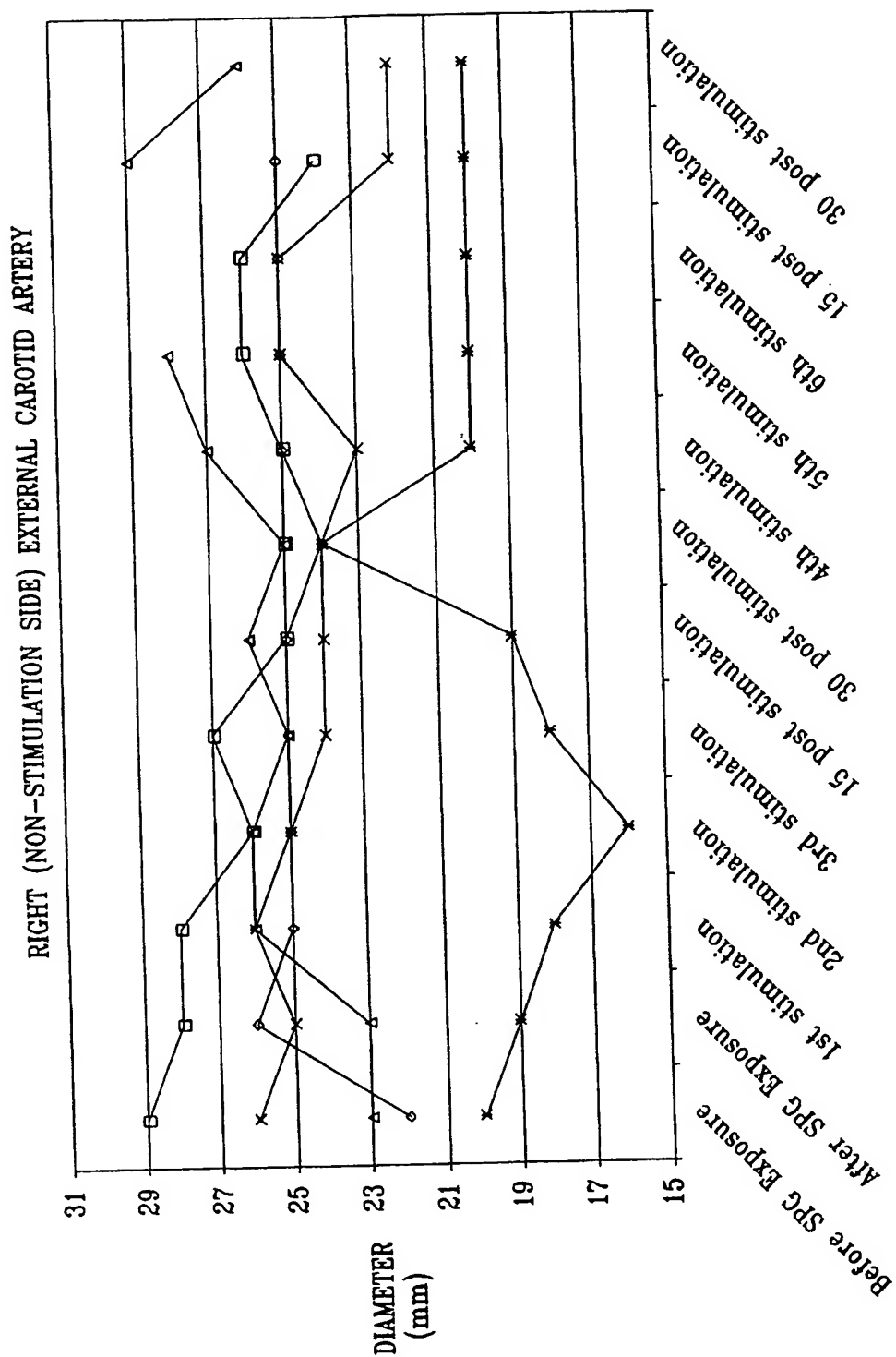
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FIG. 16D



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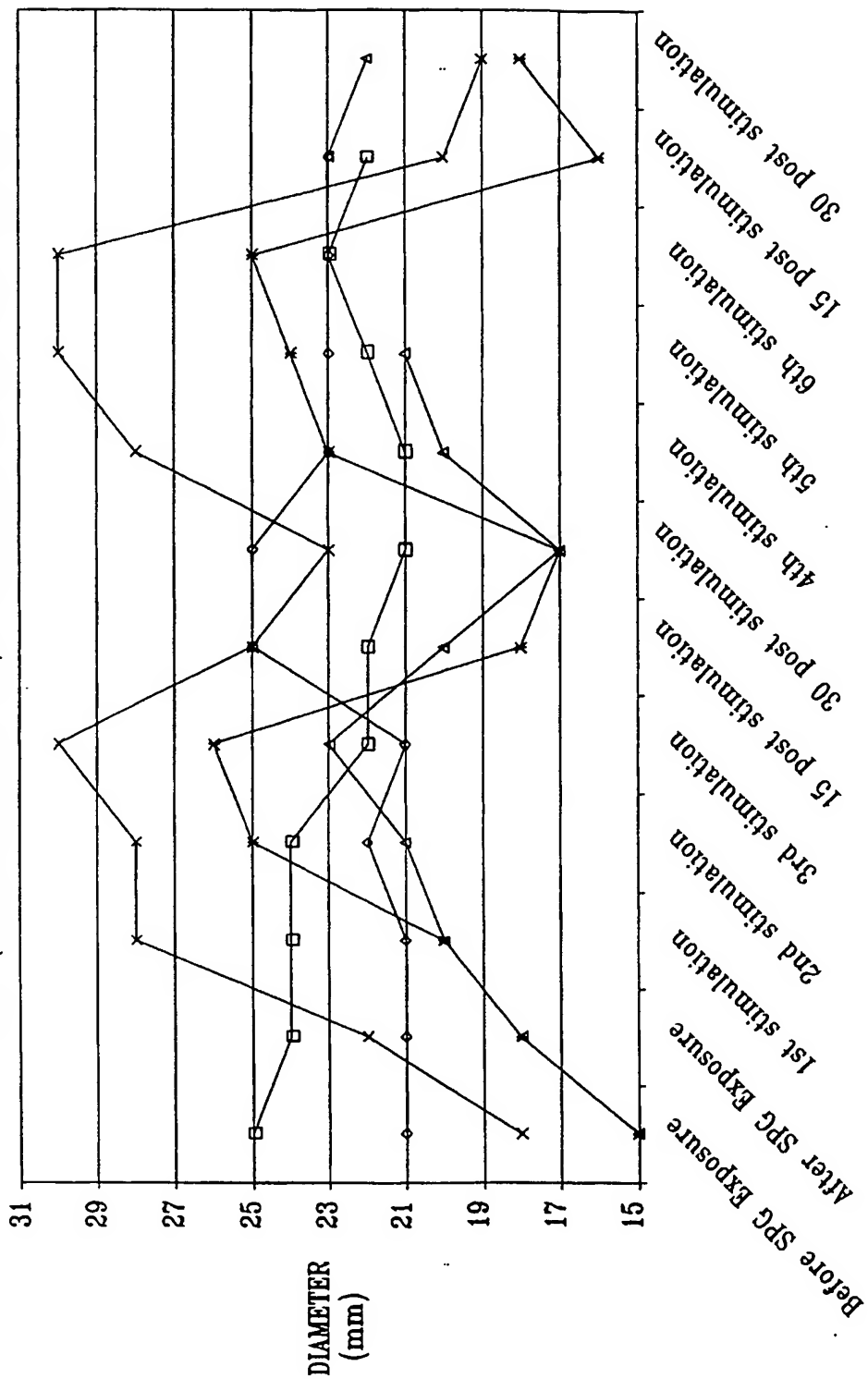
FIG. 17A



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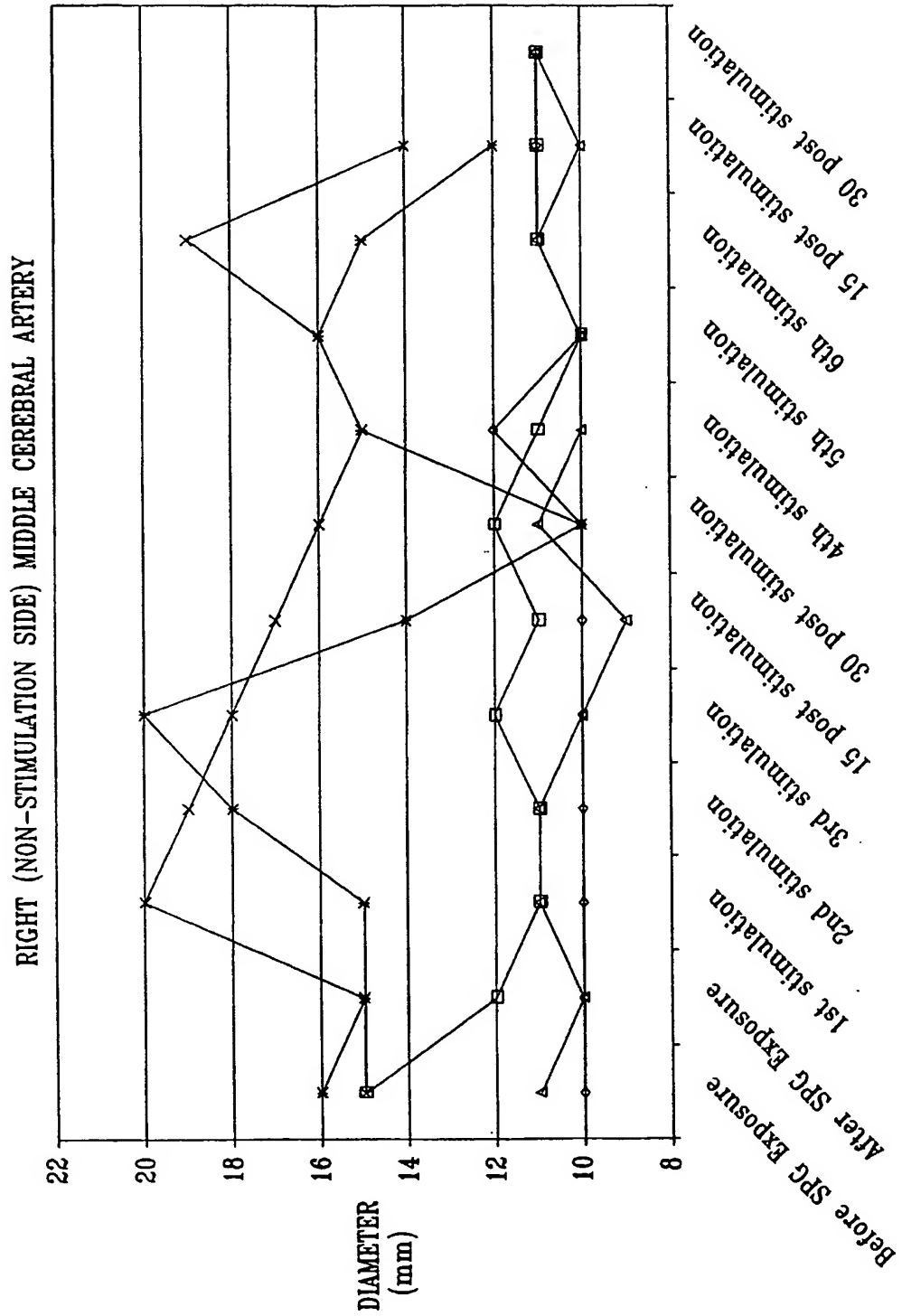
FIG. 17B

RIGHT (NON-STIMULATION SIDE) INTRACRANIAL INTERNAL CAROTID ARTERY



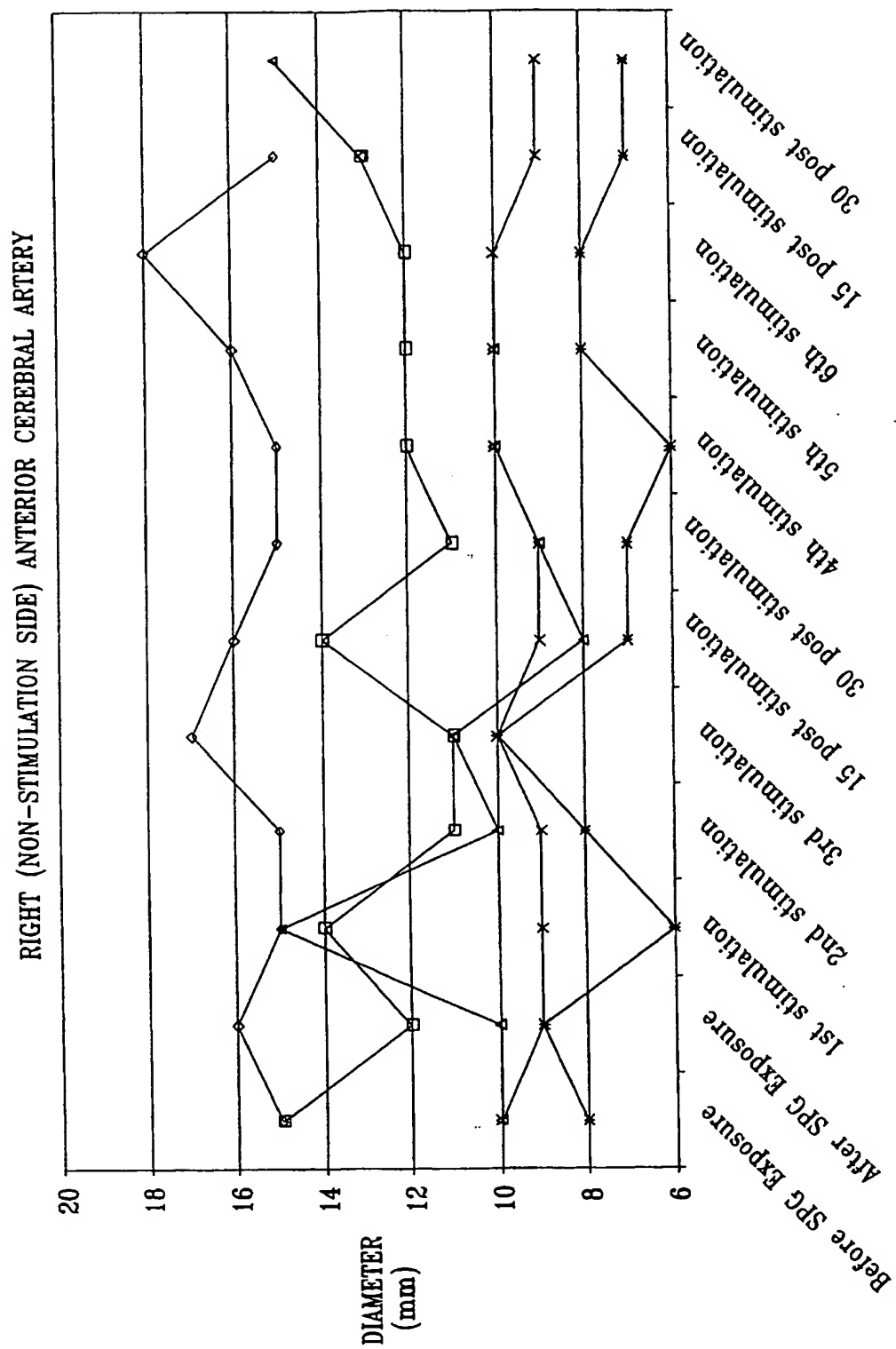
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FIG. 17C



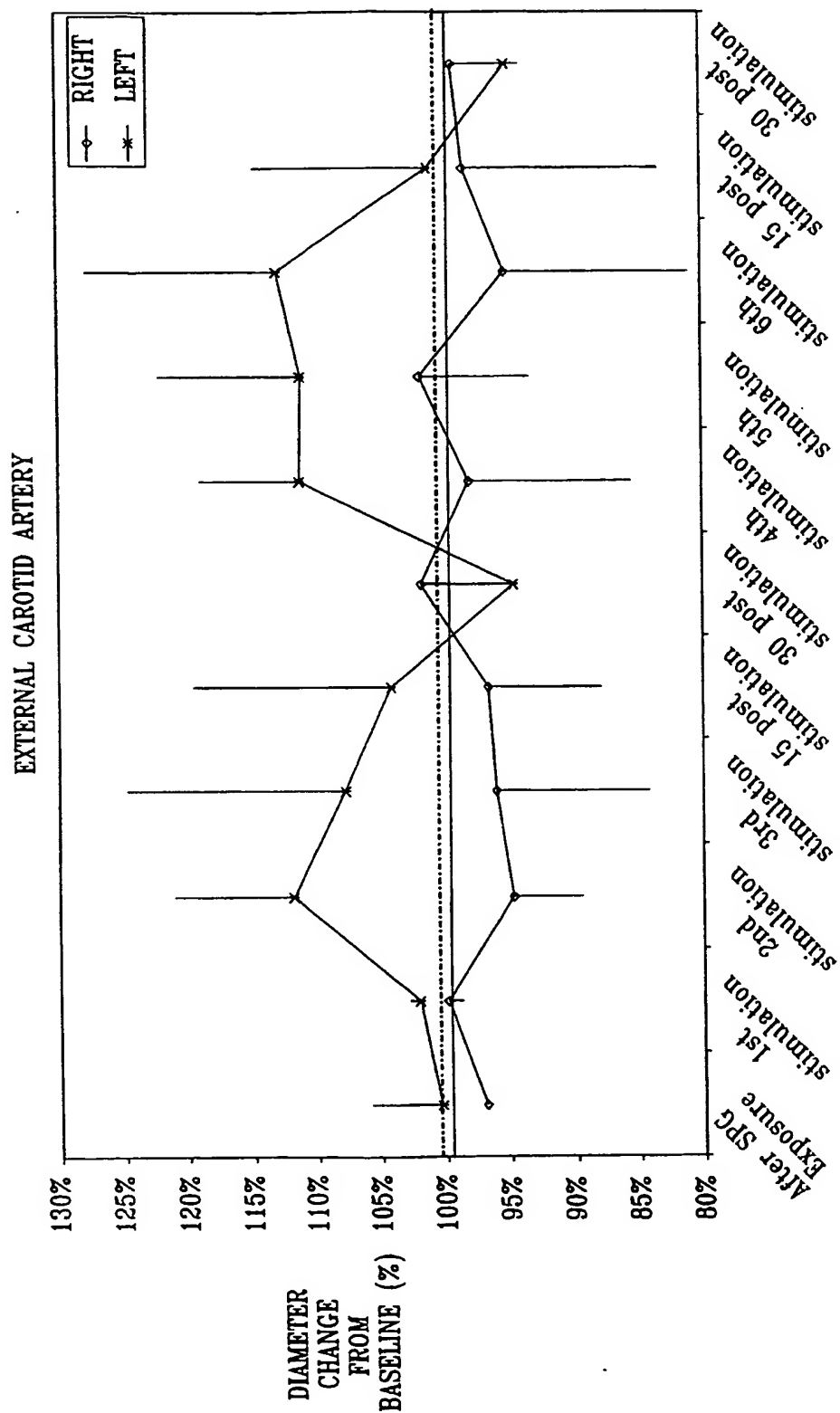
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FIG. 17D



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FIG. 18A



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FIG. 18B

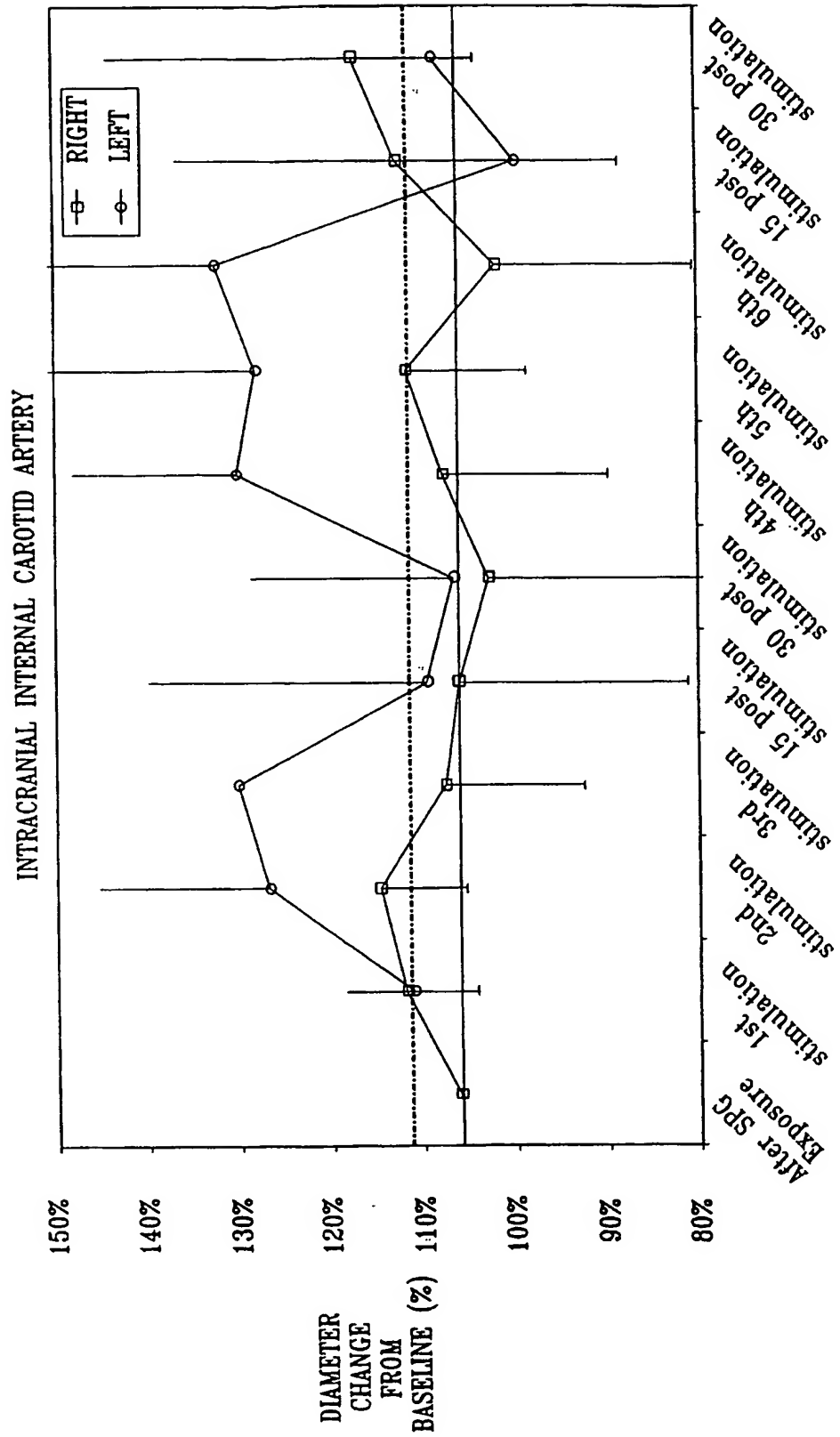
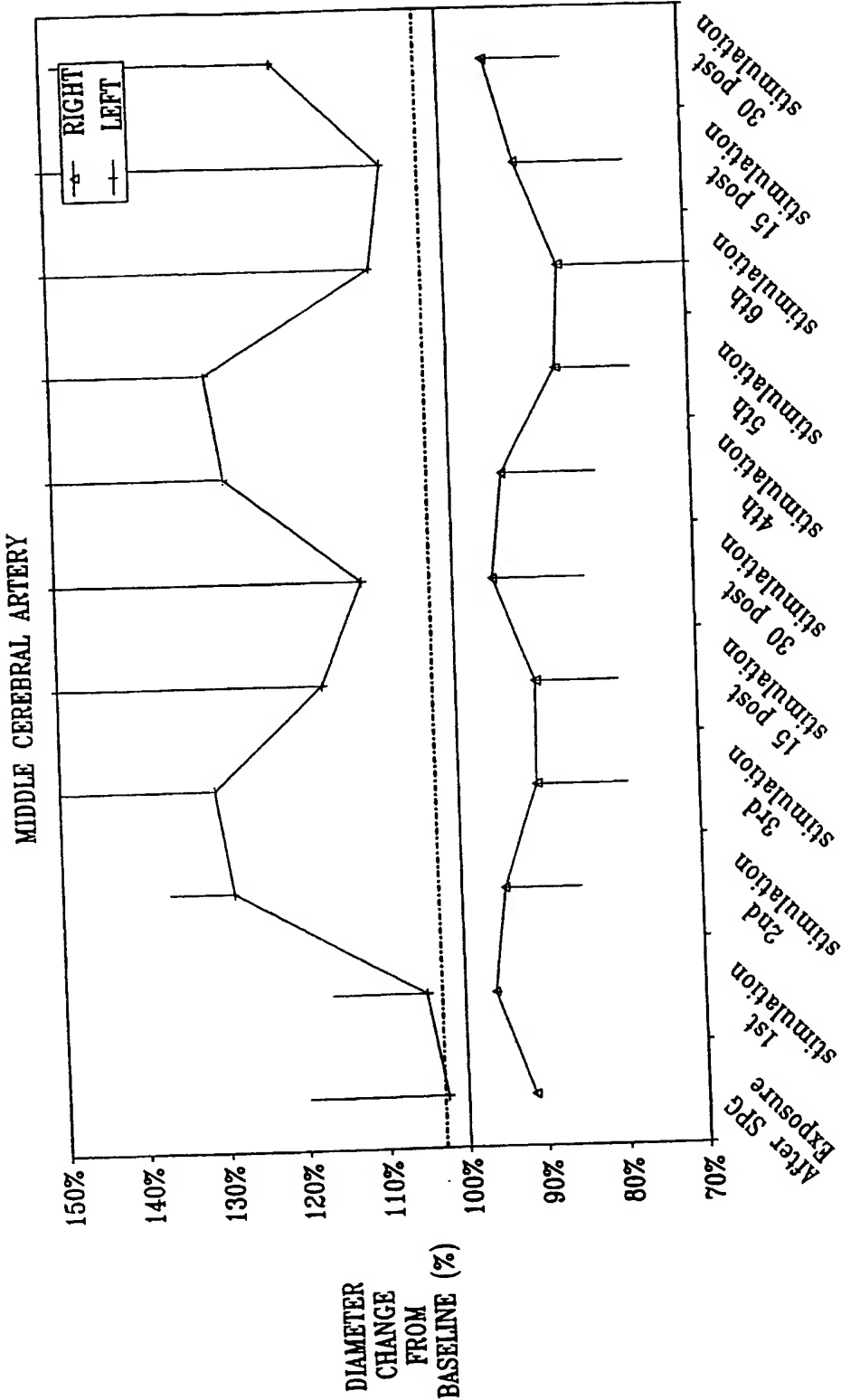
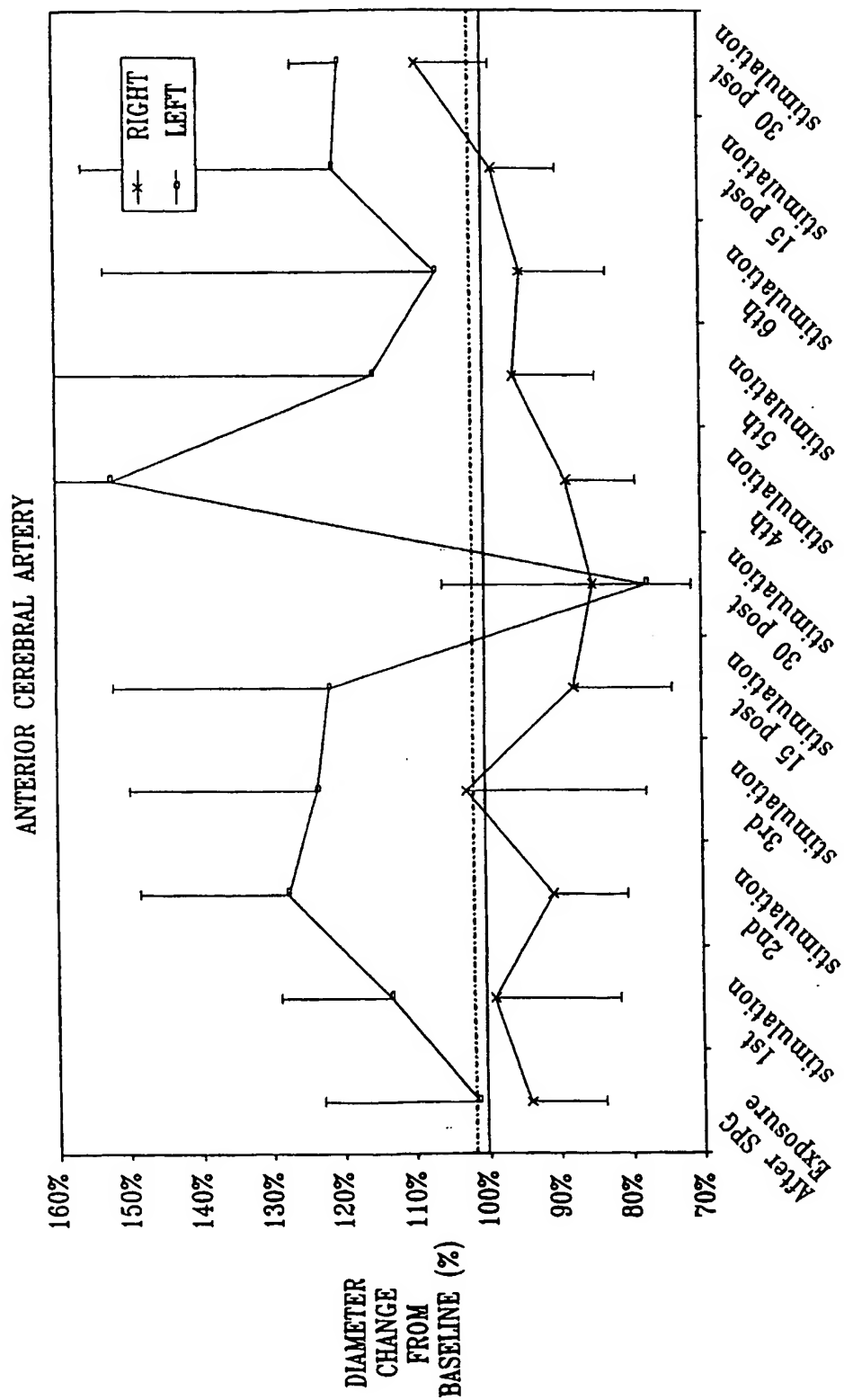


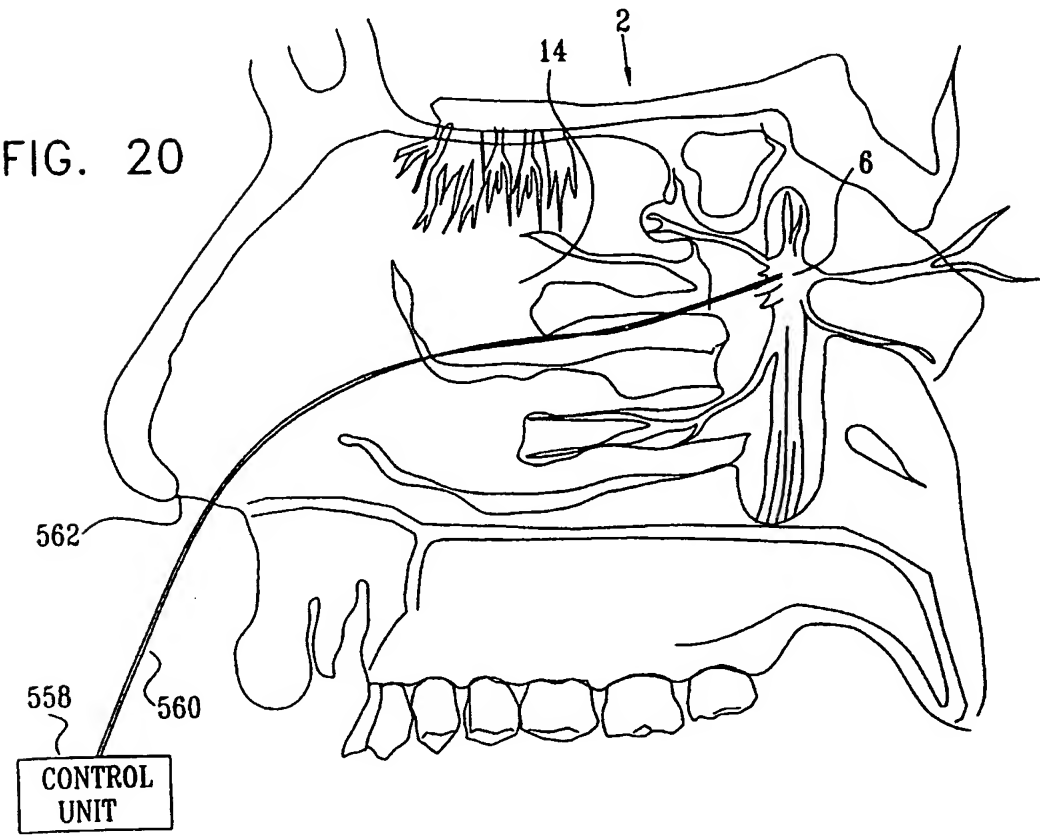
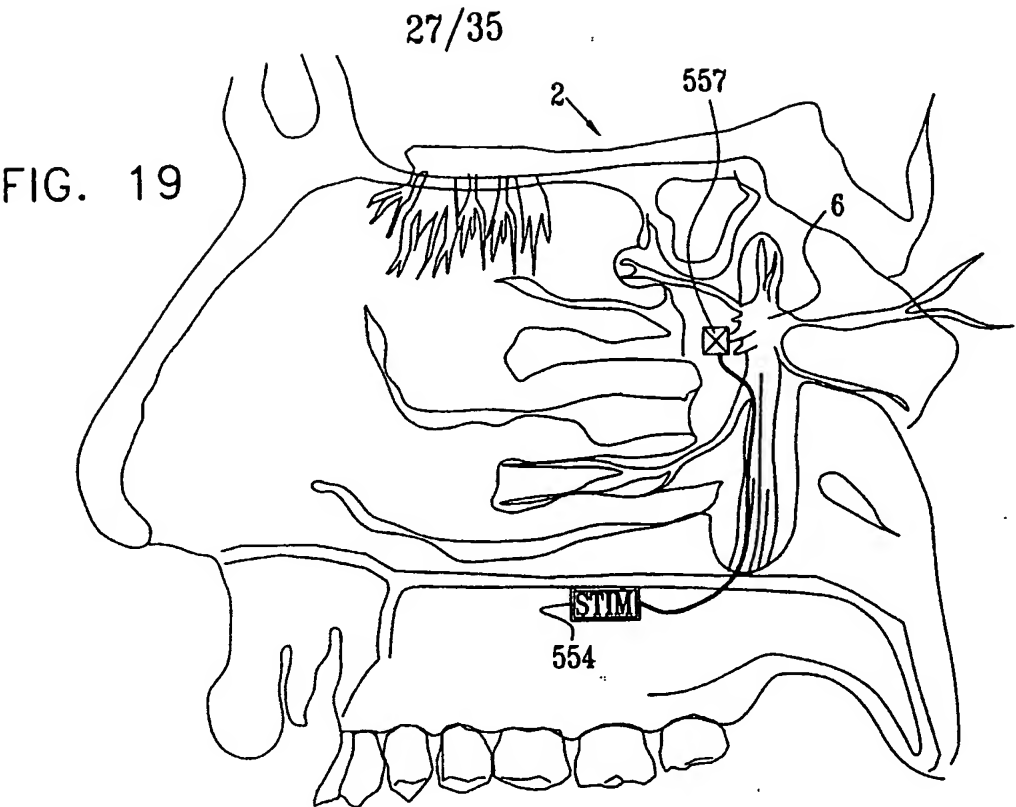
FIG. 18C



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FIG. 18D





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FIG. 21

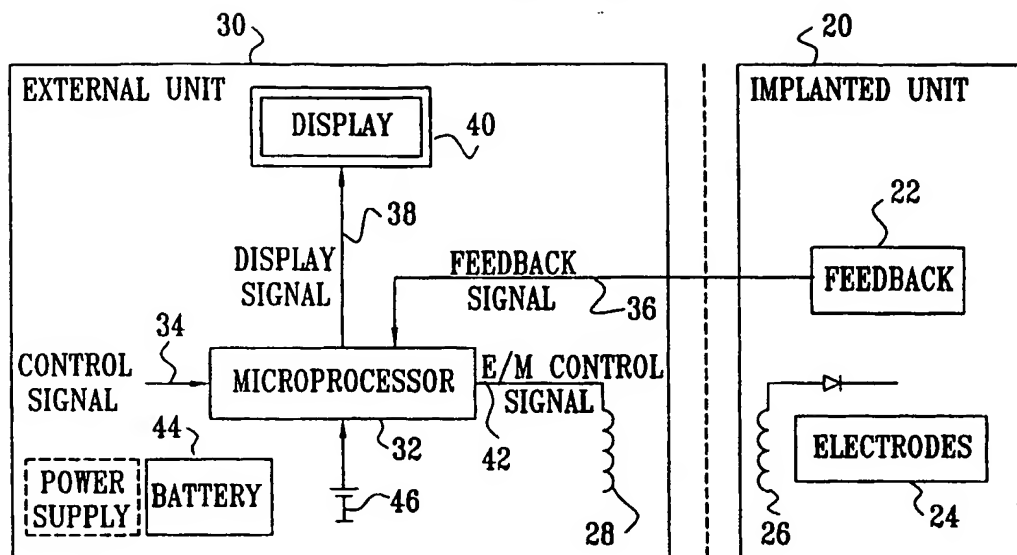
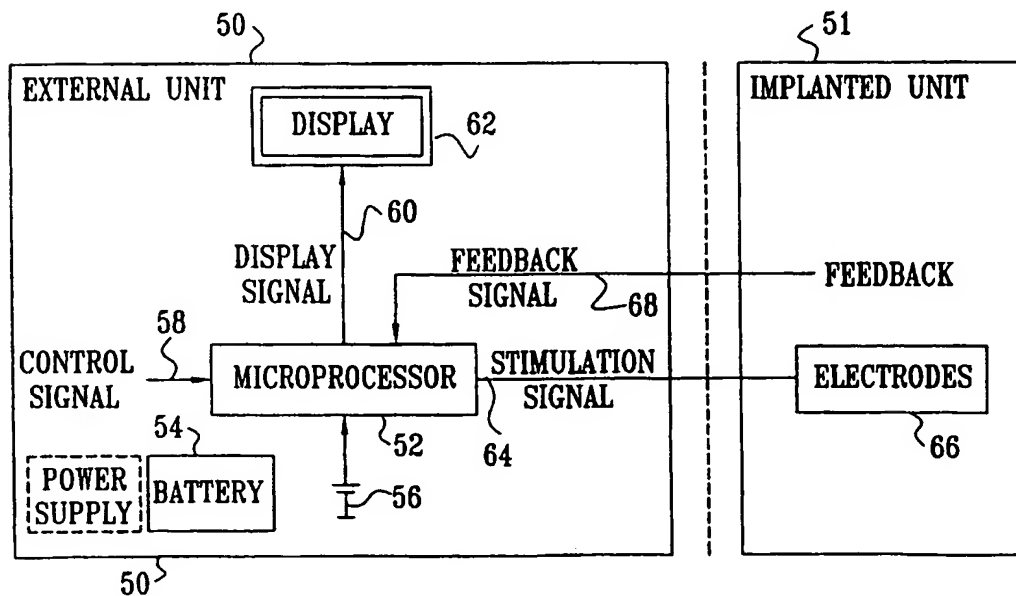


FIG. 22



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FIG. 23A

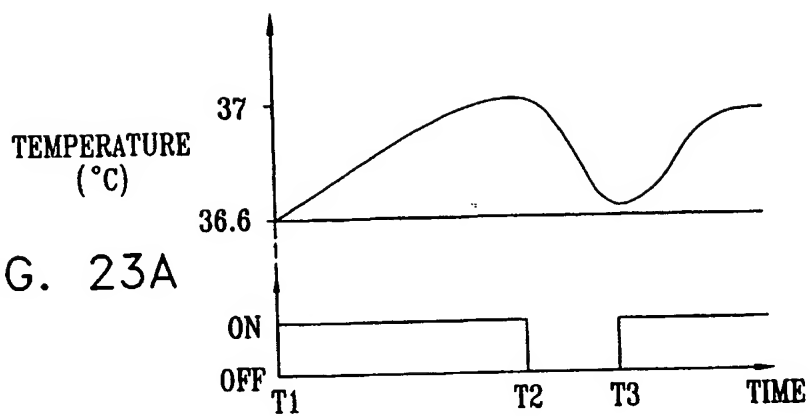


FIG. 23B

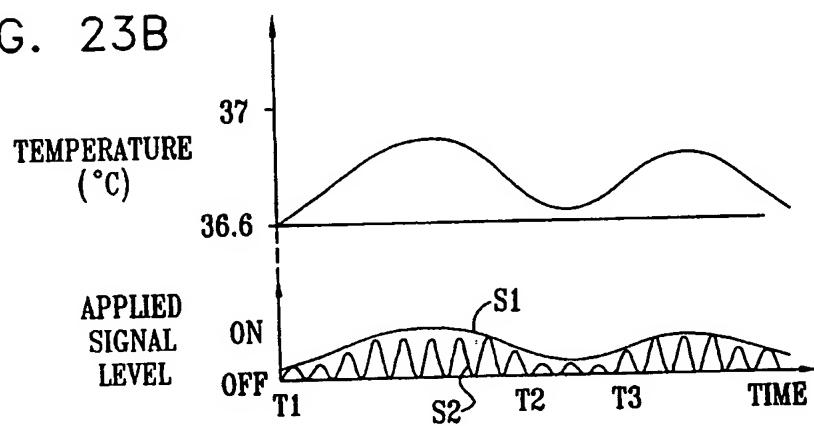
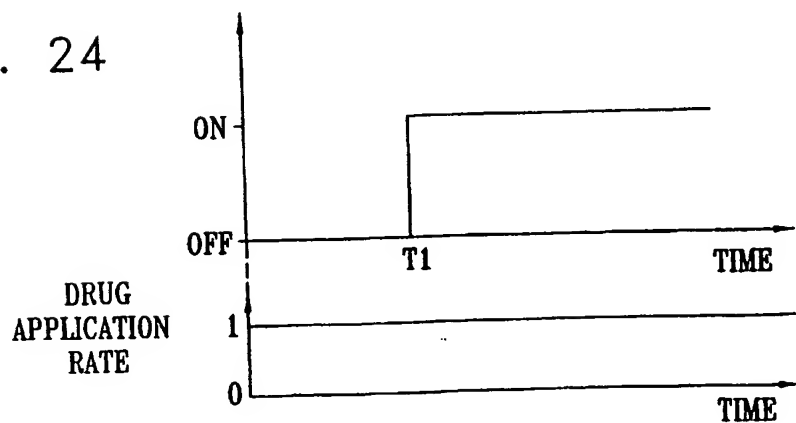


FIG. 24



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FIG. 25

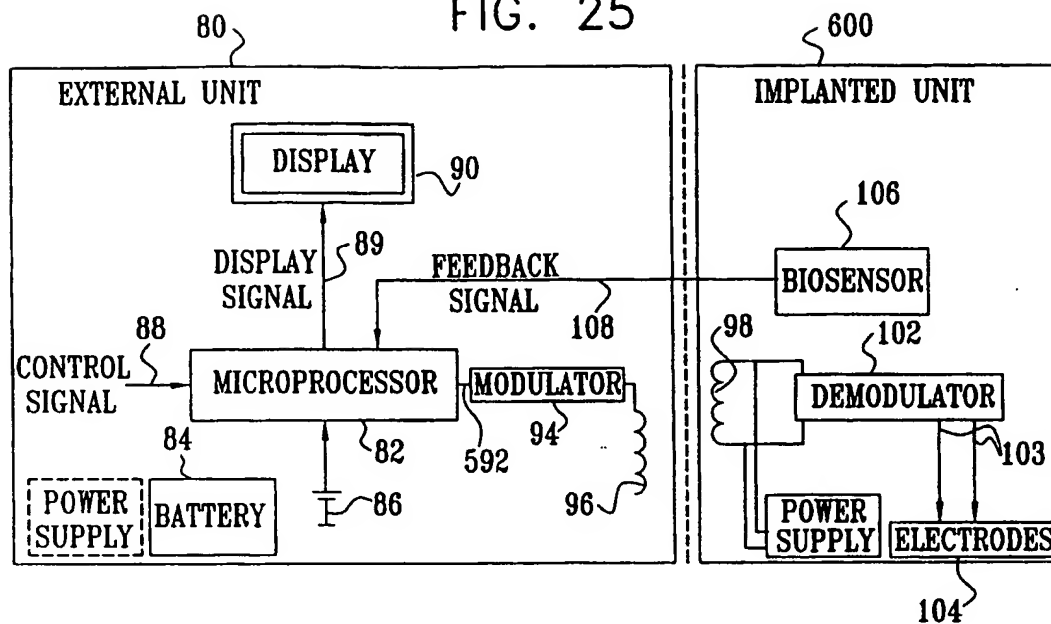


FIG. 26

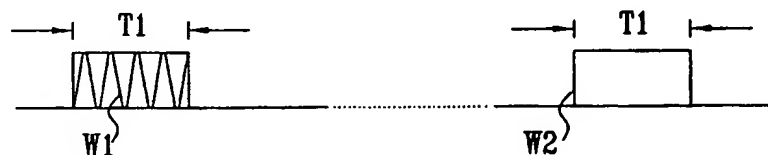
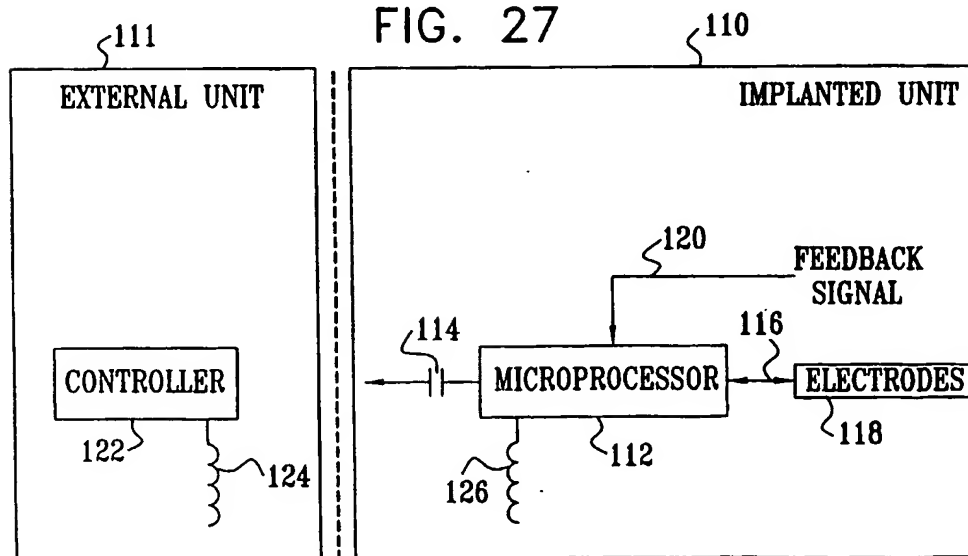


FIG. 27



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FIG. 28A

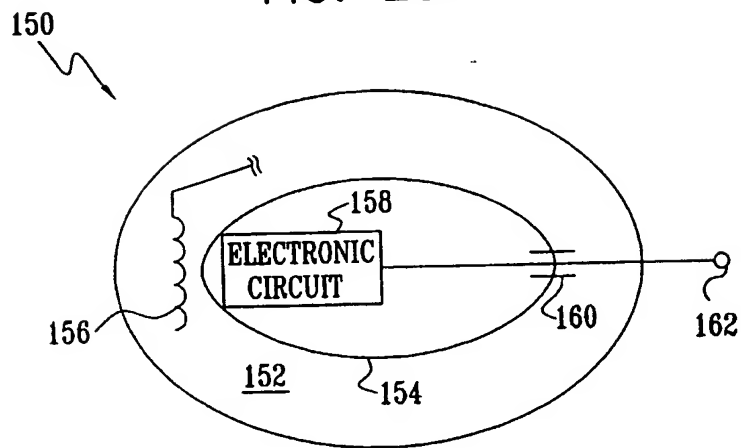
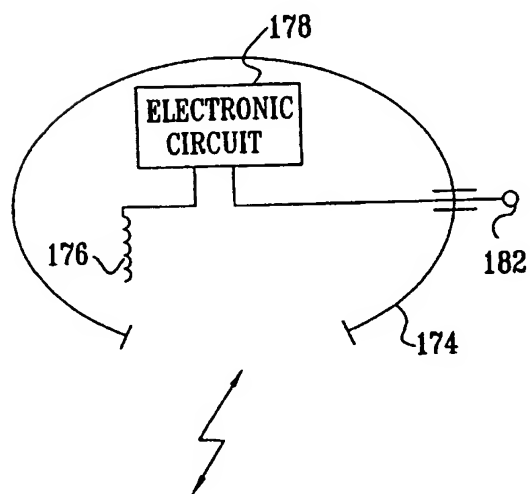


FIG. 28B



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FIG. 29

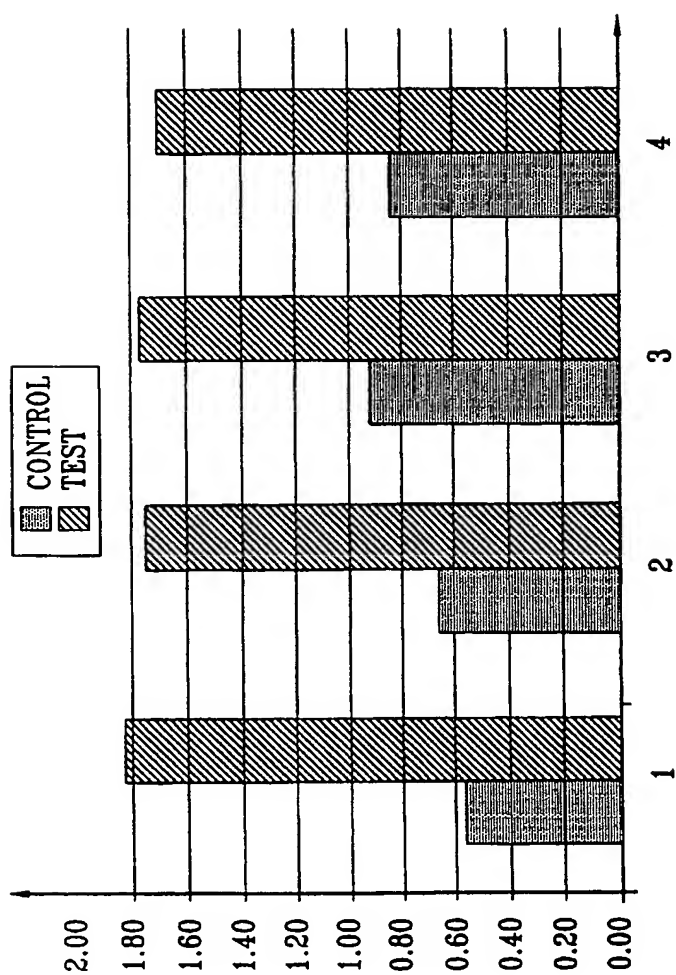


FIG. 31

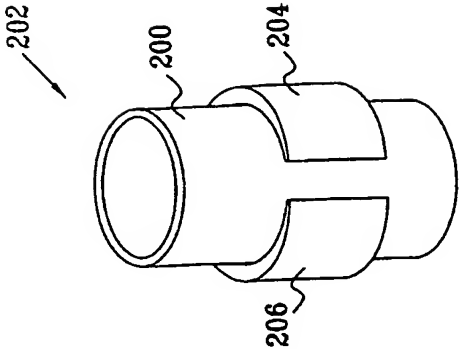
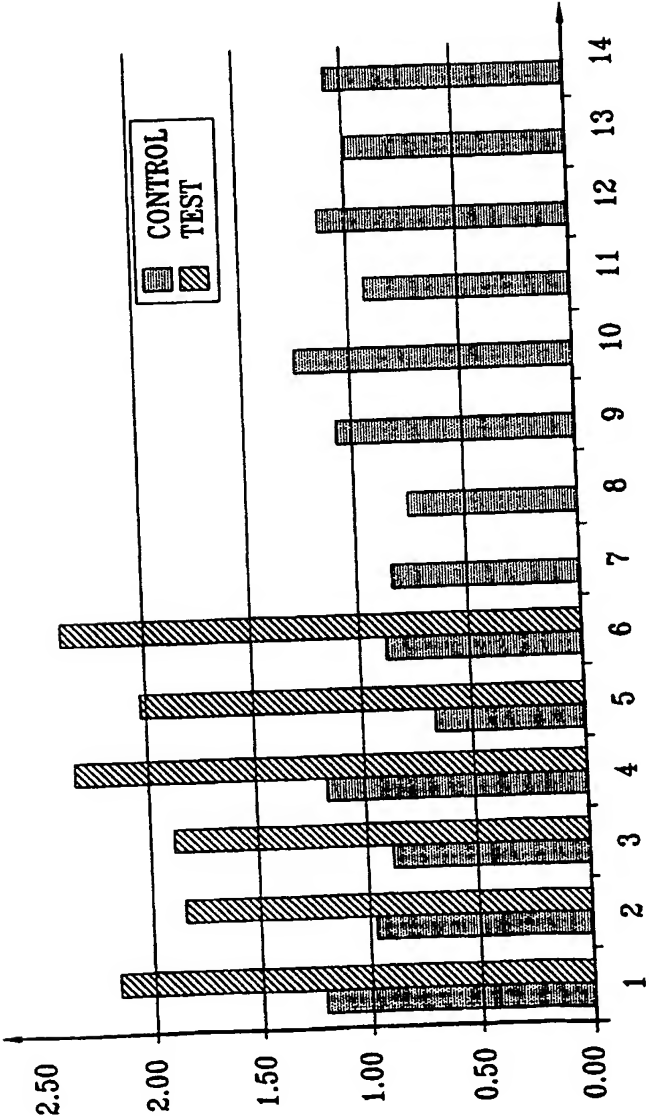
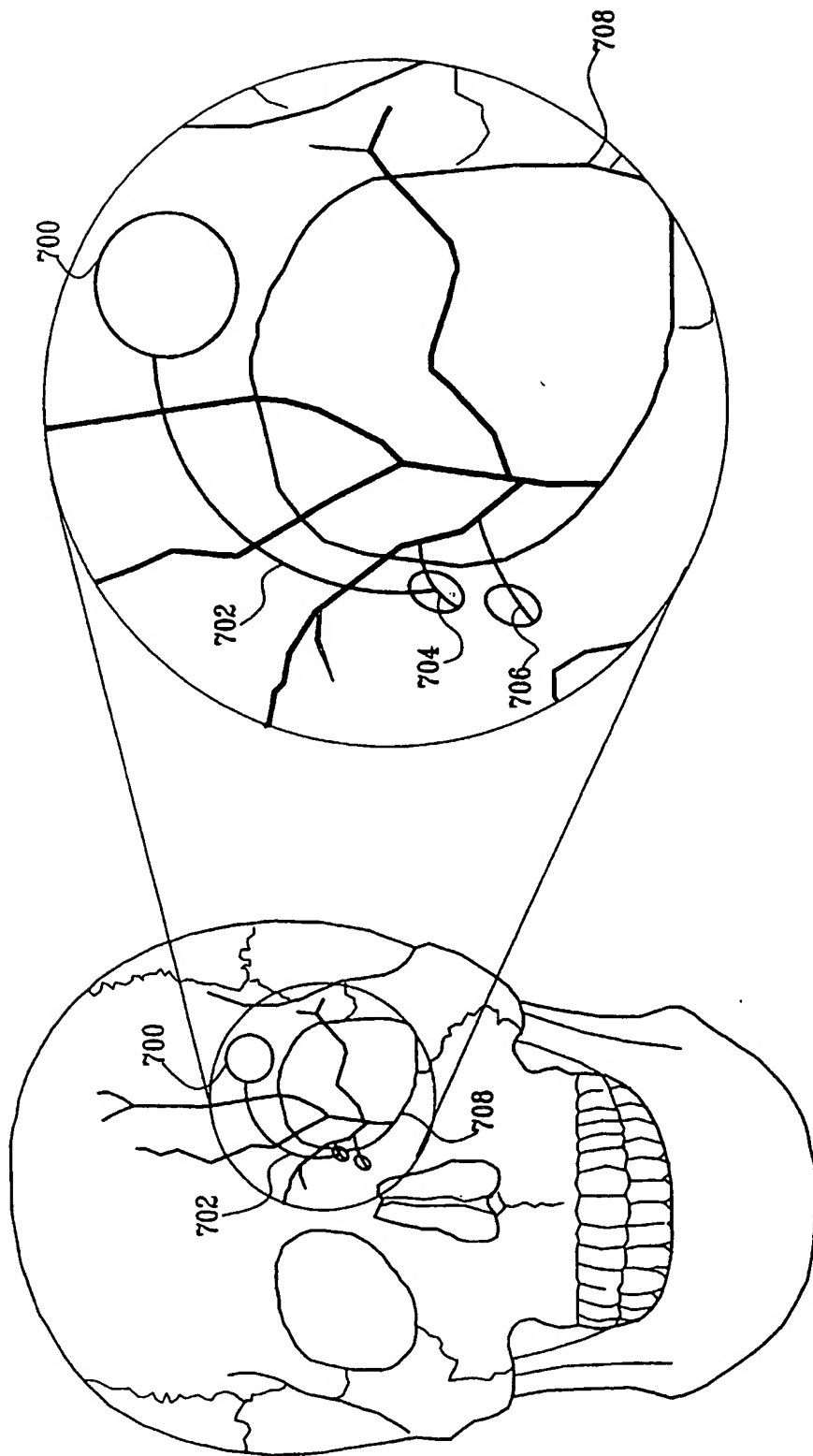


FIG. 30



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FIG. 32



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FIG. 33

